Journal of
THE CHEMICAL SOCIETY

Publication Committee

Chairman : C. K. Ingold, D.Sc., F.R.I.C., F.R.S.

G. Baddeley, Ph.D., D.Sc., F.R.I.C.
D. H. R. Barton, D.Sc., F.R.I.C., F.R.S.
C. E. H. Bawn, B.Sc., Ph.D., F.R.S.
D. J. Bell, Sc.D., Ph.D.
E. J. Bowen, M.A., D.Sc., F.R.S.
H. Burton, Ph.D., D.Sc., F.R.I.C.
J. Chatt, M.A., Ph.D., F.R.I.C.
C. A. Coulson, M.A., D.Sc., F.R.S.
H. J. Emeléus, D.Sc., A.R.C.S., F.R.S.
F. Fairbrother, D.Sc.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
B. A. Hems, D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
H. R. Ing, M.A., D.Phil., F.R.S.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
E. R. H. Jones, D.Sc., F.R.I.C., F.R.S.
F. G. Mann, Sc.D., F.R.I.C., F.R.S.
R. A. Morton, D.Sc., Ph.D., F.R.S.
R. G. W. Norrish, Sc.D., F.R.I.C., F.R.S.
L. N. Owen, Ph.D., D.Sc., F.R.I.C.
M. W. Perrin, C.B.E., M.A., F.R.I.C.
H. M. Powell, M.A., B.Sc., F.R.S.
N. Sheppard, M.A., Ph.D.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
W. F. Short, D.Sc., M.Sc.
R. Spence, C.B., Ph.D., D.Sc., F.R.I.C.
M. Stacey, Ph.D., D.Sc., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.
H. W. Thompson, M.A., D.Phil., F.R.S.
E. E. Turner, M.A., D.Sc., F.R.S.
J. Walker, Ph.D., D.Phil., D.Sc.
W. Wardlaw, C.B.E., D.Sc., F.R.I.C.
W. A. Waters, Sc.D., F.R.I.C., F.R.S.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.
A. E. Somerfield, B.A., B.Sc.

JULY, 1954

Subscription rate to non-Fellows £10 0s. 0d. per annum post free

LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1

THE CHEMICAL SOCIETY

PATRON
HER MAJESTY THE QUEEN

President
W. Wardlaw, C.B.E., D.Sc., F.R.I.C.

Vice-Presidents
who have filled the office of President

Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.
C. K. Ingold, D.Sc., F.R.I.C., F.R.S.
W. H. Mills, M.A., Sc.D., F.R.S.
Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S.
Sir Robert Robinson, O.M., D.Sc., LL.D., F.R.S.

Vice-Presidents

R. D. Haworth, D.Sc., Ph.D., F.R.S.
E. L. Hirst, D.Sc., LL.D., F.R.S.
E. R. H. Jones, D.Sc., F.R.I.C., F.R.S.
R. P. Linstead, C.B.E., M.A., D.Sc., F.R.S.
H. W. Melville, D.Sc., F.R.I.C., F.R.S.
Sir John Simonsen, D.Sc., F.R.I.C., F.R.S.

Honorary Treasurer
M. W. Perrin, C.B.E., M.A., F.R.I.C.

Honorary Secretaries

H. Burton, Ph.D., D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.

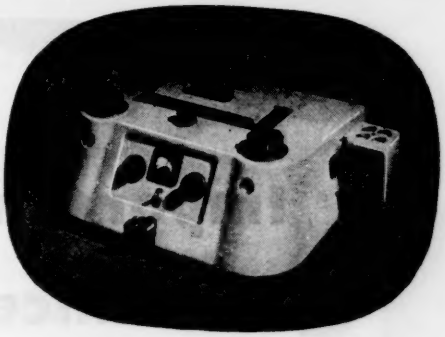
Ordinary Members of Council

C. C. Addison, D.Sc., Ph.D., F.R.I.C.
V. C. Barry, D.Sc., M.R.I.A., F.I.C.I., F.R.I.C.
D. H. R. Barton, D.Sc., F.R.I.C., F.R.S.
F. Bergel, D.Phil.Nat., D.Sc., F.R.I.C.
E. J. Bourne, Ph.D., D.Sc., A.R.I.C.
E. A. Braude, Ph.D., D.Sc., F.R.I.C.
Neil Campbell, D.Sc., Ph.D.
J. Chatt, M.A., Ph.D., F.R.I.C.
M. J. S. Dewar, M.A., D.Phil.
I. J. Faulkner, B.Sc., Ph.D., F.R.I.C.
S. J. Gregg, Ph.D., A.R.C.S., F.R.I.C.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
Brynmor Jones, Sc.D., Ph.D., F.R.I.C.
F. B. Kipping, M.A., Ph.D.
E. A. Moelwyn-Hughes, D.Phil., D.Sc., Sc.D.
A. Robertson, M.A., Ph.D., F.R.S.
J. M. Robertson, M.A., D.Sc., F.R.S.
M. A. T. Rogers, B.Sc., Ph.D., A.R.I.C.
H. N. Rydon, D.Sc., D.Phil., F.R.I.C.
H. D. Springall, M.A., D.Phil., F.R.I.C.
A. I. Vogel, D.Sc., D.I.C., F.R.I.C.

General Secretary
J. R. Ruck Keene, M.B.E., T.D., B.A.

Librarian
A. E. Cummins

Telephone Numbers : Regent 0675/6



THE Unicam SP.600 Spectrophotometer for the visible region represents a nice combination of optical and electronic design. A simple Littrow monochromator of high resolving power with a glass prism is used to give continuous wavelength selection between 3,600Å and 10,000Å in a precise and convenient manner. The vacuum photocell and amplifier have a sensitivity that allows the use of narrow slit widths with a corresponding freedom from spectral impurity. The null-point measuring system eliminates internal circuit effects and does not assume linearity of the amplifier. Alternative battery or mains operation can be provided.

The SP.600 is highly sensitive and suitable for solutions of low optical density as it will measure accurately small differences in concentration. Operation is simple and rapid, up to four samples being examined together, and readings are taken as either optical density or percentage transmission. A series of routine checks at one closely defined wavelength can be made with the same ease as a complete absorption spectrum over the wavelength range available. The spectrophotometer is strongly built, requires little maintenance and is moderately priced.

Please write for the new illustrated leaflet which describes the instrument in detail.

UNICAM
SPECTROPHOTOMETERS

UNICAM INSTRUMENTS LTD · ARBURY WORKS · CAMBRIDGE

U133B

SPECIFICATIONS FOR

H&W *GENERAL PURPOSE REAGENTS*

In recent years we have received an increasing number of requests that our general purpose chemicals should be labelled with chemical formulae or other indication of constitution, molecular weights, and particulars of purity.

We, for our part, have well appreciated that progress in science has necessitated a more enquiring attitude on the part of users of fine chemicals and the need for ready information has to be met.

Accordingly we are making immediate arrangements to print our laboratory specifications on the labels of many of our ' ordinary ' grade chemicals; that is to say those chemicals hitherto sold as ' pure,' ' recryst.' ' redistilled,' or without qualification. Formulae and molecular weights will also appear on these labels.

This scheme will be applied first to the more commonly employed substances and will be extended as rapidly as possible to cover all those chemicals that merit and can conform to such treatment. Technical or commercial grades will not be included, neither will special purpose reagents such as the POLARITAN series, Organic Reagents for Metals, and Organic Reagents for Organic Analysis.

It should perhaps be emphasized that the chemicals issued under this system are of the same quality as those previously supplied as ' ordinary ' grades; our previously existing specifications are simply being printed on the labels. The standards to which they conform are naturally of a lower level than H. & W. ' AnalaR ' chemicals which comply with the specifications issued jointly by Hopkin and Williams Ltd. and The British Drug Houses Ltd. in the well-known publication " ' AnalaR ' Standards for Laboratory Chemicals."

H&W

HOPKIN & WILLIAMS LTD.

Manufacturers of pure chemicals for Research and Analysis

FRESHWATER ROAD CHADWELL HEATH ESSEX.

For your fine Laboratory Chemicals

CONSULT WHIFFENS

Here are just a few of the laboratory chemicals available from stock:

FOR THE ANALYST

Triketohydrindene Hydrate · Murexide
o-Phenanthroline · Diazouracil · α-Naphthoflavone
sym-Trinitrobenzene

FOR THE BIOCHEMIST

Adenine · Adenosine · Guanine · Guanosine
***l*-Arginine hydrochloride · iso-Cystosine**
Dialuric Acid · *l*-Glutamine · Guanylic Acid (K Salt)
Hypoxanthine · Orotic Acid · Taurine
Thio-orotic Acid · Thiothymine · Thymine
Xanthine · Xanthosine

FOR THE RESEARCH CHEMIST

Alloxan · Alloxantin · Terephthaldehyde · Biuret
Thiophosgene · Mercaptans · Ethylene Carbonate
Propylene Carbonate

WHIFFENS

fine chemicals for industry

Full price list available on application to:—
Whiffen & Sons Ltd., North West House, Marylebone Road, London, N.W.8 · Telephone: PADdington 1041/9

Norman House, 105–109 Strand, London, W.C.2 *Telephone: Temple Bar 4455*

Divisional Offices: Walter House, Bedford St., London, W.C.2. *Tel: Temple Bar 4455.* 42 Deansgate, Manchester. *Tel: Deansgate 6451.* Clarence Chambers, 39 Corporation St., Birmingham 2. *Tel: Midland 6954.* 28 St. Enoch Square, Glasgow, C.1. *Tel: Glasgow Central 9561.* 53 Middle Abbey St., Dublin. *Tel: Dublin 45775.* 35–37 Boyne Square, Belfast. *Tel: Belfast 20081.*

AT REIGATE

OUR JOB

AS ESSENCE MANUFACTURERS

IS TO TAKE NATURAL PRODUCTS WHICH HAVE A FLAVOUR OR AROMA OR BOTH; EXTRACT FROM THEM THE PRINCIPLES RESPONSIBLE FOR THAT FLAVOUR AND AROMA, AND THEN PREPARE THESE PRINCIPLES IN SUCH A FORM AS TO BE EASILY AND CONVENIENTLY AND ECONOMICALLY USED BY OUR CUSTOMERS.

WE ARE SPECIALISTS IN THIS FIELD AND CAN OFFER GUARANTEED NATURAL PRODUCTS WHICH FOR QUALITY AND TRUE FLAVOUR ARE IN A CLASS BY THEMSELVES.

REIGATE BRAND—

VANILLA NATURA
GRAPEFRUIT NATURA
ORANGE NATURA
(SWEET OR BITTER)
ORRIS NATURA

WHITE, TOMKINS & COURAGE, LTD.
NORTH ALBERT WORKS, REIGATE

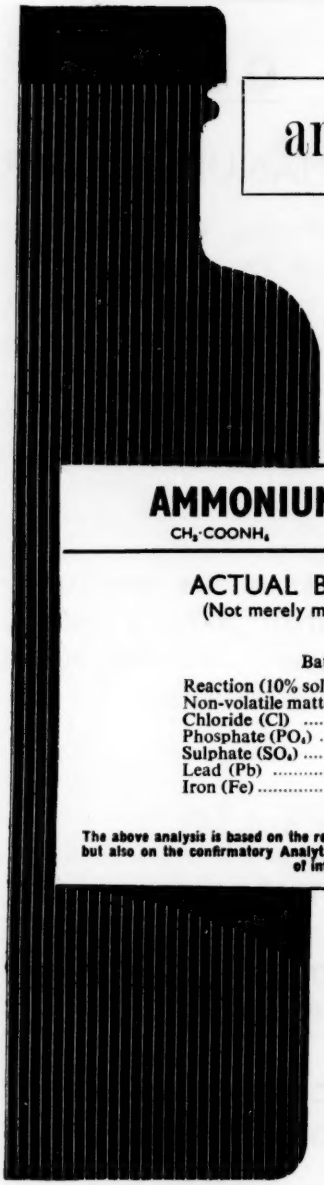
TELEGRAMS: ESSWHITE, REIGATE TELEPHONE: REIGATE 2242-3

ESTABLISHED 1841

Judactan

analytical reagents

with actual batch analysis



AMMONIUM ACETATE A.R.

$CH_3 \cdot COONH_4$ Mol. Wt. 77·08

ACTUAL BATCH ANALYSIS
(Not merely maximum impurity values)

Batch No. 10531

Reaction (10% solution)	pH6·7
Non-volatile matter	0·0025%
Chloride (Cl)	0·0003%
Phosphate (PO_4)	0·0002%
Sulphate (SO_4)	0·0015%
Lead (Pb)	0·00006%
Iron (Fe)	0·00005%

The above analysis is based on the results, not of our own Control Laboratories alone, but also on the confirmatory Analytical Certificate issued by independent Consultants of international repute

Chemists all over the world are grateful for our care. Our policy of having independent analyses made gives chemists added confidence in their work.

Why not compare the actual batch analysis shown with the purities guaranteed by the specifications to which you normally work? You will find the comparison of interest and almost certainly of help to you.

The General Chemical & Pharmaceutical Co. Ltd., Chemical Manufacturers, Judex Works, Sudbury, Middlesex.

CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

The Separation and Purification of Americium-241 and the Absorption Spectra of Tervalent and Quinquevalent Americium Solutions.
By G. R. HALL and P. D. HERNIMAN 2214

The Heats of Formation of Complex Ions containing Ethylenediamine.
By T. DAVIES, (MISS) S. S. SINGER, and L. A. K. STAVELEY 2304

Thermochemistry of Organo-boron Compounds. Part IV. Dimethylaminochloroborines.
By H. A. SKINNER and N. B. SMITH 2324

Investigations on the Co-ordinative Power of Uranyl. Part I. The Preparation and Properties of Uranyl Complexes of Certain β-Diketones.
By L. SACCONI and (MISS) G. GIANNONI 2368

Studies in the Chemistry of Quadrivalent Germanium : Ion-exchange Studies of Solutions of Germanates.
By D. A. EVEREST and J. E. SALMON 2438

The Quenching of the Fluorescence of Anthracene Gas.
By W. S. METCALF 2485

Di-*tert.*-butylberyllium and Beryllium Hydride.
By G. E. COATES and F. GLOCKLING 2526

The Cyanogen Halides. Part III. Their Heats of Formation and Free Energies.
By G. LORD and A. A. WOOLF 2546

The Distribution of Ruthenium Tetroxide between Carbon Tetrachloride and Aqueous Alkali, Acid, and Neutral Salt Solutions.
By F. S. MARTIN 2564

The Kinetics of Oxidation by Nitrous Acid and Nitric Acid. Part I. Oxidation of Formic Acid by Nitrous Acid.
By JEAN V. L. LONGSTAFF and K. SINGER. 2604

The Kinetics of Oxidation by Nitrous Acid and Nitric Acid. Part II. Oxidation of Formic Acid in Aqueous Nitric Acid.
By JEAN V. L. LONGSTAFF and K. SINGER. 2610

NOTES :

The Magnetic Susceptibility of Lanthanum.
By O. M. HILAL and F. A. SALEH 2635

The Surface Tension of Antimony Pentafluoride.
By D. R. HUB and P. L. ROBINSON 2640

The Cryoscopic Behaviour of Non-electrolytes in Sulphuric Acid.
By P. A. H. WYATT 2647

Physical Organic.

Oxidation Studies. Part I. Metal-catalysed Persulphate Oxidation of Some Simple Phenols.
By R. G. R. BACON, R. GRIME, and D. J. MUNRO 2275

Kinetics and Mechanism of Aromatic Halogenation by Hypohalous Acids. Part I. Bromination of Aromatic Ethers by Hypobromous Acid.
By S. J. BRANCH and BRYNMOR JONES 2317

Physical Properties and Thermodynamic Functions of Trichloroacetonitrile.
By MANSEL DAVIES and DAVID G. JENKIN 2374

Steric Relations between Ionisation of Aralkyl Chlorides and Dissociation of Anilinium Ions. Part I.
By G. BADDELEY, J. CHADWICK, and H. T. TAYLOR 2405

Stages in Oxidations of Organic Compounds by Potassium Permanganate. Part IV. Oxidation of Malonic Acid and its Analogues.
By ALAN Y. DRUMMOND and WILLIAM A. WATERS 2456

PAGE

The Promotion of Raney Nickel Catalysts.
By Robert B. Blance and David T. Gibson 2487

The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part VI. Solvolysis and the accompanying Rearrangement of 1 : 1- and of 3 : 3-Dimethylallyl Chloride.
By P. B. D. de la Mare and C. A. Vernon 2504

The Kinetics of Chlorohydrin Formation. Part V. The Reaction between Hypochlorous Acid and Crotonic Acid in Buffered Solutions at 25° and 35°.
By D. A. Craw 2510

The Kinetics of Chlorohydrin Formation. Part VI. The Reaction between Hypochlorous Acid and Tiglic Acid at Constant pH.
By D. A. Craw 2515

The Reaction Velocity of Some Substituted *o*- and *p*-Chloronitrobenzenes with Piperidine.
By Jorge A. Brieux and Venancio Deulofeu 2519

The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part IV. The Dipole Moments of the 2 : 2′-Dihalogeno- and 2 : 2′- and 3 : 3′-Dinitrodiphenyls.
By A. C. Littlejohn and J. W. Smith 2552

Mesomorphism and Chemical Constitution. Part III. The Effect of Halogen Substitution on the Mesomorphism of the 4-Alkoxybenzoic Acids.
By G. W. Gray and Brynmor Jones 2556

The Pyrolysis of Chloroalkenes. Part I. Allyl Chloride.
By (Miss) A. M. Goodall and K. E. Howlett 2596

The Pyrolysis of Chloroalkenes. Part II. Trichloroethylene.
By (Miss) A. M. Goodall and K. E. Howlett 2599

Notes :

The Exchange of Iodine Atoms between Iodine and Methyl Iodide in the Temperature Range 150—375°.
By Douglas Clark, H. O. Pritchard, and A. F. Trotman-Dickenson . . 2633

The Dielectric Constant of Trifluoroacetic Anhydride and Related Compounds.
By J. M. Tedder 2646

Organic.

Oxidation Products of Di*iso*butylene. Part I. Liquid-phase Oxidation of Di*iso*butylene : Formation, Properties, and Analysis of 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane.
By E. J. Gasson, A. F. Millidge, G. R. Primavesi, W. Webster, and D. P. Young 2161

Oxidation Products of Di*iso*butylene. Part II. The Isomerisation of 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane, and Some Products derived from 2 : 4 : 4-Trimethylpentanal.
By E. J. Gasson, A. R. Graham, A. F. Millidge, I. K. M. Robson, W. Webster, A. M. Wild, and D. P. Young 2170

Oxidation Products of Di*iso*butylene. Part III. Products from Ring-opening of 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane.
By A. R. Graham, A. F. Millidge, and D. P. Young 2180

Organic Peroxides. Part III. The Preparation of Alkyl Hydroperoxides and Dialkyl Peroxides. Characteristic Derivatives of Alkyl Hydroperoxides.
By A. G. Davies, R. V. Foster, and A. M. White 2200

Organic Peroxides. Part IV. Alkyl–Oxygen Heterolysis in Organic Peroxides.
By A. G. Davies, R. V. Foster, and R. Nery 2204

12-Oxygenated Pregnane Derivatives. Part II. Preparation of 21-Acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione from Hecogenin.
By (Mrs.) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and (Mrs.) I. A. Stuart-Webb 2209

The Cyclization of Substituted *N*-Thiocarbamoylglycines, and Some *mero*Cyanine Dyes derived from the Products.
By R. A. Jeffreys. 2221

Steroids and Walden Inversion. Part XII. The Epimeric 3-Cholesterylacetic and 3-Cholestanylacetic Acids.
By C. W. Shoppee and R. J. Stephenson. 2230

Aromatic Azo-Compounds. Part VI. The Action of Light on Azoxy-Compounds.
By G. M. Badger and R. G. Buttery 2243

PAGE

The Aporphine Series. Part I. Developments of the Bischler–Napieralski–Pschorr Synthetic Method. The Synthesis of (±)-*iso*Bulbocapnine and (±)-Actinodaphnine Methyl Ether.
By D. H. Hey and L. C. Lobo 2246

The Near-ultra-violet Absorption Spectra of Some Heterocyclic Compounds. Part I. Benzoxazoles.
By R. Passerini 2256

The Near-ultra-violet Absorption Spectra of Some Heterocyclic Compounds. Part II. Benzothiazoles.
By A. Cerniani and R. Passerini 2261

Clovene and β-Caryophyllene Alcohol.
By Albert W. Lutz and Evans B. Reid 2265

The Organic Chemistry of Phosphorus. Part II. The Action of Triphenyl Phosphite Dihalides on Alcohols: Two Further New Methods for the Preparation of Alkyl Halides.
By D. G. Coe, S. R. Landauer, and H. N. Rydon 2281

Nucleotides. Part XXVIII. A Synthesis of Uridine-5′ Triphosphate (UTP).
By G. W. Kenner, A. R. Todd, R. F. Webb, and F. J. Weymouth 2288

The Preparation and Properties of Some Derivatives of 1-Phenylpyrazole.
By I. L. Finar and K. E. Godfrey 2293

12-Oxygenated Pregnane Derivatives. Part III. Ketals of *allo*Pregnane-12 : 20-diones.
By (Mrs.) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and (Mrs.) I. A. Stuart-Webb 2298

Reactions of Diphenyl Phosphates of Δ^5-Sterols.
By J. H. Turnbull and Walter Wilson 2301

Cyclisation of Benzamido-derivatives of 1 : 1′-Dianthraquinonylamine to Derivatives of 1 : 2-7 : 8-Diphthaloylcarbazole.
By William Bradley and Jeffrey V. Butcher. 2311

Acyclic Derivatives of Amino-sugars.
By M. W. Whitehouse, P. W. Kent, and C. A. Pasternak 2315

Polynuclear Heterocyclic Systems. Part VIII. Synthetic Applications of the Schmidt Reaction.
By G. M. Badger and J. H. Seidler 2329

Steroids. Part XIV. 7 : 8-Epoxides of 9α- and 9β-Ergostan-11-one Derivatives.
By James Grigor, William Laird, Duncan Maclean, G. T. Newbold, and F. S. Spring 2333

Introduction of the 11-Oxo- and the 11α-Hydroxy-group into Ring c Unsubstituted Steroids. Part IX. The Epoxides of $\Delta^{7:9(11)}$-5α-Hydroxysapogenins.
By Carl Djerassi, A. J. Lemin, G. Rosenkranz, and Franz Sondheimer . . 2346

Reducing Action of Glycols in Alkaline Medium. Part I. Mechanism of Formation of Stilbenes from Substituted Benzaldehydes.
By Wadie Tadros, Labib Ekladius, and Alfy Badie Sakla 2351

Heterocyclic Nitrogen Compounds. Part IV. Further Condensations with Aldehydic Acids and Diamines.
By (Miss) E. F. M. Stephenson 2354

Derivatives of 2-Alkoxy-8-amino-1 : 5-naphthyridines
By A. A. Goldberg, R. S. Theobald, and W. Williamson 2357

Studies in the Alicyclic Series. Part I. 1-Benzoyl*cyclo*alkenes as Acceptors in the Michael Condensation.
By David Ginsburg 2361

Studies on Fructosans. Part V. Short-chain Fructosans from *Lolium perenne*.
By V. D. Harwood, R. A. Laidlaw, and R. G. J. Telfer 2364

The Amination of Anthraquinone with Hydroxylamine in Sulphuric Acid.
By A. C. Robson and Samuel Coffey 2372

Colouring Matters of the Aphididæ. Part XI. Pigments from *Hamamelistes* Species.
By S. F. MacDonald 2378

Studies on Phosphorylation. Part XII. Selective Anionic Dealkylation of Neutral Esters of Phosphoric and Thiophosphoric Acids.
By J. Lecocq and A. R. Todd 2381

PAGE

The Chemistry of the Triterpenes and Related Compounds. Part XXIV. The Conversion of Polyporenic Acid A into a Lanosterol Derivative.
By T. G. Halsall and R. Hodges 2385

Nitramines and Nitramides. Part VII. The Irreversible Decomposition of Nitroguanidine and of Nitrourea by Sulphuric Acid.
By C. Holstead and Alex. H. Lamberton 2391

Immunopolysaccharides. Part II. Structure of a *Betacoccus arabinosaceous* Dextran.
By S. A. Barker, E. J. Bourne, G. T. Bruce, W. B. Neely, and M. Stacey . 2395

The Chemistry of Hop Constituents. Part VI. The Structure of Cohumulone.
By G. A. Howard and A. R. Tatchell 2400

Cyto-active Amino-acid and Peptide Derivatives. Part I. Substituted Phenylalanines.
By F. Bergel and J. A. Stock 2409

The Rearrangement of Some *N*-Substituted Hydrazobenzenes.
By G. R. Clemo and T. B. Lee 2417

The Elimination of Non-angular Alkyl Groups in Aromatisation Reactions. Part III.
By Wesley Cocker and D. S. Jenkinson 2420

Hydrazine. Part VIII. Some Salts of 3 : 5 : 5-Trimethyl-Δ^2-pyrazoline and of 3 : 5 : 5-Trimethyl-1-*iso*propylidene-Δ^2-pyrazolinium Ion. (With Notes on the Optical Properties of the Crystals. By H. C. G. Vincent.)
By W. Pugh 2423

Hydrazine. Part IX. Condensation Products of Aldehydes and Ketones with Salts of Some Substituted Δ^2-Pyrazolines and Hydrazines.
By M. Lamchen, W. Pugh, and A. M. Stephen. 2429

The Cyclisation of Some Substituted Phenylsuccinic Acids.
By V. Askam and W. H. Linnell 2435

Products from the Alkaline and Reductive Fission of the Epoxide Ring of Methyl 3 : 4- and 2 : 3-Anhydro-6-deoxy-α-L-taloside and of their Methylated Derivatives.
By George Charalambous and Elizabeth Percival 2443

Antimalarial 2-Alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes.
By D. M. Besly and A. A. Goldberg 2448

The Reduction of Anthraquinone and other Polycyclic Quinones with Aluminium Alkoxides (Meerwein–Pondorff Reagent).
By Samuel Coffey and (Miss) V. Boyd 2468

Internuclear Cyclisation. Part IX. Abnormal Reactions of 2-Amino-*N*-methylbenzanilides containing *ortho*-Substituents.
By D. H. Hey and D. G. Turpin 2471

Internuclear Cyclisation. Part X. The Preparation of 3 : 4-Benzocoumarin.
By R. A. Heacock and D. H. Hey 2481

Conjugated Macrocycles. Part XXV. Cross-conjugated Macrocycles with Inner Great Rings of 16, 20, and 24 Atoms.
By P. F. Clark, J. A. Elvidge, and R. P. Linstead 2490

Optical Activity in 1-Phenylnaphthalene-2′-carboxylic Acid and Related Compounds.
By D. Muriel Hall, S. Ridgwell, and E. E. Turner 2498

The Hemicelluloses of Scots Pine (*Pinus sylvestris*) and Black Spruce (*Picea nigra*) Woods.
By A. R. N. Gorrod and J. K. N. Jones 2522

The Synthesis and Reactions of Branched-chain Hydrocarbons. Part III. α-Hydroxyketones with Secondary and Tertiary Alkyl Groups.
By W. J. Hickinbottom, A. A. Hyatt, and M. B. Sparke 2529

The Synthesis and Reactions of Branched-chain Hydrocarbons. Part IV. The Synthesis of Ketones with Quaternary Carbon Atoms.
By W. J. Hickinbottom, A. A. Hyatt, and M. B. Sparke 2533

Synthesis of 10-Hydroxy-4 : 5 : 6-trimethoxyaporphine.
By T. R. Govindachari and K. Nagarajan 2537

The Reaction of Chloroacetone with Aryl Grignard Reagents.
By R. L. Huang 2539

4-Aminosalicylaldehyde.
By A. A. Goldberg and H. A. Walker 2540

Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part XIII. The Behaviour of Certain *N*- and *NN′*-Alkylated Benzidines towards Oxidising Agents.
By R. Belcher, A. J. Nutten, and W. I. Stephen 2543

PAGE

Studies on *Xanthorrhoea* Resins. Part I. Isolation of Chrysophanic Acid (1 : 8-Dihydroxy-3-methylanthraquinone) and of 2′ : 4-Dihydroxy-4′-methoxychalkone.
By HEINZ DUEWELL 2562

Synthetic Œstrogens. Part II. The Synthesis of Tetra-alkyldibenzyls and Substituted Succinonitriles by Free-radical Dimerisation.
By R. L. HUANG and LEE KUM-TATT 2570

Preparation of Phenothiazine Derivatives as Possible Anthelmintics.
By ALEXANDER MACKIE and A. ANTHONY CUTLER 2577

The Constitution of Yohimbine and Related Alkaloids. Part VII. Synthesis of 5 : 6 : 7 : 8-Tetrahydro*iso*quinoline-3-carboxylic Acid.
By R. M. ANDERSON, G. R. CLEMO, and G. A. SWAN 2579

Syntheses in the Indole Series.
By G. R. CLEMO and J. C. SEATON 2582

Griseofulvin. Part IX. Isolation of the Bromo-analogue from *Penicillium griseofulvum* and *Penicillium nigricans*.
By J. MACMILLAN 2585

Mycobactin. A Growth Factor for *Mycobacterium johnei*. Part II. Degradation, and Identification of Fragments.
By G. A. SNOW 2588

Perhydroindanes. Part IV. Some 1-Substituted Hexahydroindanes.
By L. E. COLES, W. H. LINNELL, DAVID W. MATHIESON, and A. S. SHOUKRI. . 2617

The Gum of *Acacia pycnantha*.
By E. L. HIRST and A. S. PERLIN 2622

The Synthesis of Progesterone and Related Compounds
By A. F. DAGLISH, J. GREEN, and V. D. POOLE 2627

NOTES :

2 : 2′ : 4 : 4′ : 5 : 5′-Hexamethoxydiphenyl.
By W. I. TAYLOR 2636

Condensation of α-Keto-acids with 2-3′ : 4′-Dihydroxyphenylethylamine.
By J. S. LITTLE, A. G. SMITH, W. I. TAYLOR, and B. R. THOMAS 2636

The Methanolysis of Some Acetyl Derivatives of Cevine.
By W. J. ROSENFELDER 2638

The Reduction of 4-Amino- and 4-Acetamido-salicylic Acids.
By A. A. GOLDBERG and R. S. THEOBALD 2641

Methylation of Indoles.
By K. T. POTTS and J. E. SAXTON 2641

The Preparation and Freezing Point of Pure Naphthalene.
By E. F. G. HERINGTON, A. B. DENSHAM, and P. J. MALDEN 2643

Methyl 3β-Iodochol-5-enate.
By W. KLYNE 2644

The Structure of the Oxazoline Derivatives of Glucose and Galactose.
By J. C. P. SCHWARZ 2644

The Steroid Series. Part III. Alteration to Nomenclature.
By D. H. HEY, JOHN HONEYMAN, and W. J. PEAL 2648

Synthetic Œstrogens.
By J. GRUNDY 2649

CENTENARY LECTURE :

Some Applications of the Separation of Large Molecules and Colloidal Particles.
By ARNE TISELIUS 2650

TILDEN LECTURE :

The Chemistry of Intermolecular Compounds.
By H. M. POWELL 2658

OBITUARY NOTICES :

JOHN SAMUEL STAFFORD BRAME 2664
COLIN CAMPBELL 2664
GERTRUDE MAUD ROBINSON 2667

INDEX OF AUTHORS' NAMES.

Adams, W. J., Kirk, D. N., Patel, D. K., Petrow, V., and Stuart-Webb, I. A., 2209, 2298.
Anderson, R. M., Clemo, G. R., and Swan, G. A., 2579.
Askam, V., and Linnell, W. H., 2435.
Bacon, R. G. R., Grime, R., and Munro, D. J., 2275.
Baddeley, G., Chadwick, J., and Taylor, H. T., 2405.
Badger, G. M., and Buttery, R. G., 2243.
Badger, G. M., and Seidler, J. H., 2329.
Barker, S. A., Bourne, E. J., Bruce, G. T., Neely, W. B., and Stacey, M., 2395.
Belcher, R., Nutten, A. J., and Stephen, W. I., 2543.
Bergel, F., and Stock, J. A., 2409.
Besly, D. M., and Goldberg, A. A., 2448.
Blance, R. B., and Gibson, D. T., 2487.
Bourne, E. J. See Barker, S. A., 2395.
Boyd, V. See Coffey, S., 2468.
Bradley, W., and Butcher, J. V., 2311.
Branch, S. J., and Jones, B., 2317.
Brieux, J. A., and Deulofeu, V., 2519.
Bruce, G. T. See Barker, S. A., 2395.
Butcher, J. V. See Bradley, W., 2311.
Buttery, R. G. See Badger, G. M., 2243.
Cerniani, A., and Passerini, R., 2261.
Chadwick, J. See Baddeley, G., 2405.
Charalambous, G., and Percival, E., 2443.
Clark, D., Pritchard, H. O., and Trotman-Dickenson, A. F., 2633.
Clark, P. F., Elvidge, J. A., and Linstead, R. P., 2490.
Clemo, G. R., and Lee, T. B., 2417.
Clemo, G. R., and Seaton, J. C., 2582.
Clemo, G. R. See also Anderson, R. M., 2579.
Coates, G. E., and Glockling, F., 2526.
Cocker, W., and Jenkinson, D. S., 2420.
Coe, D. G., Landauer, S. R., and Rydon, H. N., 2281.
Coffey, S., and Boyd, V., 2468.
Coffey, S. See also Robson, A. C., 2372.
Coles, L. E., Linnell, W. H., Mathieson, D. W., and Shoukri, A. S., 2617.
Craw, D. A., 2510, 2515.
Cutler, A. A. See Mackie, A., 2577.
Daglish, A. F., Green, J., and Poole, V. D., 2627.
Davies, A. G., Foster, R. V., and Nery, R., 2204.
Davies, A. G., Foster, R. V., and White, A. M., 2200.
Davies, M., and Jenkin, D. G., 2374.
Davies, T., Singer, S. S., and Staveley, L. A. K., 2304.
de la Mare, P. B. D., and Vernon, C. A., 2504.
Densham, A. B. See Herington, E. F. G., 2643.
Deulofeu, V. See Brieux, J. A., 2519.
Djerassi, C., Lemin, A. J., Rosenkranz, G., and Sondheimer, F., 2346.
Drummond, A. Y., and Waters, W. A., 2456.
Duewell, H., 2562.
Ekladius, L. See Tadros, W., 2351.
Elvidge, J. A. See Clark, P. F., 2490.
Everest, D. A., and Salmon, J. E., 2438.
Finar, I. L., and Godfrey, K. E., 2293.
Foster, R. V. See Davies, A. G., 2200, 2204.
Gasson, E. J., Graham, A. R., Millidge, A. F., Robson, I. K. M., Webster, W., Wild, A. M., and Young, D. P., 2170.
Gasson, E. J., Millidge, A. F., Primavesi, G. R., Webster, W., and Young, D. P., 2161.
Giannoni, G. See Sacconi, L., 2368.
Gibson, D. T. See Blance, R. B., 2487.
Ginsburg, D., 2361.
Glockling, F. See Coates, G. E., 2426.
Godfrey, K. E. See Finar, I. L., 2293.
Goldberg, A. A., and Theobald, R. S., 2641.
Goldberg, A. A., Theobald, R. S., and Williamson, W., 2357.
Goldberg, A. A., and Walker, H. A., 2540.
Goldberg, A. A. See also Besly, D. M., 2448.
Goodall, A. M., and Howlett, K. E., 2596, 2599.
Gorrod, A. R. N., and Jones, J. K. N., 2522.
Govindachari, T. R., and Nagarajan, K., 2537.
Graham, A. R., Millidge, A. F., and Young, D. P., 2180.
Graham, A. R. See also Gasson, E. J., 2170.
Gray, G. W., and Jones, B., 2556.
Green, J. See Daglish, A. F., 2627.
Grigor, J., Laird, W., Maclean, D., Newbold, G. T., and Spring, F. S., 2333.
Grime, R. See Bacon, R. G. R., 2275.
Grundy, J., 2649.
Hall, D. M., Ridgwell, S., and Turner, E. E., 2498.
Hall, G. R., and Herniman, P. D., 2214.
Halsall, T. G., and Hodges, R., 2385.
Harwood, V. D., Laidlaw, R. A., and Telfer, R. G. J., 2364.
Heacock, R. A., and Hey, D. H., 2481.
Herington, E. F. G., Densham, A. B., and Malden, P. J., 2643.
Herniman, P. D. See Hall, G. R., 2214.
Hey, D. H., Honeyman, J., and Peal, W. J., 2648.
Hey, D. H., and Lobo, L. C., 2246.
Hey, D. H., and Turpin, D. G., 2471.
Hey, D. H. See also Heacock, R. A., 2481.
Hickinbottom, W. J., Hyatt, A. A., and Sparke, M. B., 2529, 2533.
Hilal, O. M., and Saleh, F. A., 2635.
Hirst, E. L., and Perlin, A. S., 2622.
Hodges, R. See Halsall, T. G., 2385.
Holstead, C., and Lamberton, A. H., 2391.
Honeyman, J. See Hey, D. H., 2648.
Howard, G. A., and Tatchell, A. R., 2400.
Howlett, K. E. See Goodall, A. M., 2596, 2599.
Huang, R. L., 2539.
Huang, R. L., and Kum-Tatt, L., 2570.
Hub, D. R., and Robinson, P. L., 2640.
Hyatt, A. A. See Hickinbottom, W. J., 2529, 2533.
Jeffreys, R. A., 2221.
Jenkin, D. G. See Davies, M., 2374.
Jenkinson, D. S. See Cocker, W., 2420.
Jones, B. See Branch, S. J., 2317, and Gray, G. W., 2556.
Jones, J. K. N. See Gorrod, A. R. N., 2522.
Kenner, G. W., Todd, A. R., Webb, R. F., and Weymouth, F. J., 2288.
Kent, P. W. See Whitehouse, M. W., 2315.
Kirk, D. N. See Adams, W. J., 2209, 2298.
Klyne, W., 2644.
Kum-Tatt, L. See Huang, R. L., 2570.
Laird, W. See Grigor, J., 2333.
Laidlaw, R. A. See Harwood, V. D., 2364.
Lamberton, A. H. See Holstead, C., 2391.
Lamchen, M., Pugh, W., and Stephen, A. M., 2429.
Landauer, S. R. See Coe, D. G., 2281.

Lecocq, J., and Todd, A. R., 2381.
Lee, T. B. See Clemo, G. R., 2417.
Lemin, A. J. See Djerassi, C., 2346.
Little, J. S., Smith, A. G., Taylor, W. I., and Thomas, B. R., 2636.
Littlejohn, A. C., and Smith, J. W., 2552.
Linnell, W. H. See Askam, V., 2435, and Coles, L. E., 2617.
Linstead, R. P. See Clark, P. F., 2490.
Lobo, L. C. See Hey, D. H., 2246.
Longstaff, J. V. L., and Singer, K., 2604, 2610.
Lord, G., and Woolf, A. A., 2546.
Lutz, A. W., and Reid, E. B., 2265.
MacDonald, S. F., 2378.
Mackie, A., and Cutler, A. A., 2577.
Maclean, D. See Grigor, J., 2333.
MacMillan, J., 2585.
Malden, P. J. See Herington, E. F. G., 2643.
Martin, F. S., 2564.
Mathieson, D. W. See Coles, L. E., 2617.
Metcalf, W. S., 2485.
Millidge, A. F. See Gasson, E. J., 2161, 2170, and Graham, A. R., 2180.
Munro, D. J. See Bacon, R. G. R., 2275.
Nagarajan, K. See Govindachari, T. R., 2537.
Neely, W. B. See Barker, S. A., 2395.
Nery, R. See Davies, A. G., 2204.
Newbold, G. T. See Grigor, J., 2333.
Nutten, A. J. See Belcher, R., 2543.
Passerini, R., 2256.
Passerini, R. See Cerniani, A., 2261.
Pasternak, C. A. See Whitehouse, M. W., 2315.
Patel, D. K. See Adams, W. J., 2209, 2298.
Peal, W. J. See Hey, D. H., 2648.
Percival, E. See Charalambous, G., 2443.
Perlin, A. S. See Hirst, E. L., 2622.
Petrow, V. See Adams, W. J., 2209, 2298.
Poole, V. D. See Daglish, A. F., 2627.
Potts, K. T., and Saxton, J. E., 2641.
Primavesi, G. R. See Gasson, E. J., 2161.
Pritchard, H. O. See Clark, D., 2633.
Pugh, W., 2423.
Pugh, W. See Lamchen, M., 2429.
Reid, E. B. See Lutz, A. W., 2265.
Ridgwell, S. See Hall, D. M., 2498.
Robinson, P. L. See Hub, D. R., 2640.
Robson, A. C., and Coffey, S., 2372.
Robson, I. K. M. See Gasson, E. J., 2170.
Rosenfelder, W. J., 2638.
Rosenkranz, G. See Djerassi, C., 2346.
Rydon, H. N. See Coe, D. G., 2281.
Sacconi, L., and Giannoni, G., 2368.
Sakla, A. B. See Tadros, W., 2351.
Saleh, F. A. See Hilal, O. M., 2635.
Salmon, J. E. See Everest, D. A., 2438.
Saxton, J. E. See Potts, K. T., 2641.
Schwarz, J. C. P., 2644.
Seaton, J. C. See Clemo, G. R., 2582.
Seidler, J. H. See Badger, G. M., 2329.
Shoppee, C. W., and Stephenson, R. J., 2230.
Shoukri, A. S. See Coles, L. E., 2617.
Singer, K. See Longstaff, J. V. L., 2604, 2610.
Singer, S. S. See Davies, T., 2304.
Skinner, H. A., and Smith, N. B., 2324.
Smith, A. G. See Little, J. S., 2636.
Smith, J. W. See Littlejohn, A. C., 2552.
Smith, N. B. See Skinner, H. A., 2324.
Snow, G. A., 2588.
Sondheimer, F. See Djerassi, C., 2346.
Sparke, M. B. See Hickinbottom, W. J., 2529, 2533.
Spring, F. S. See Grigor, J., 2333.
Stacey, M. See Barker, S. A., 2395.
Staveley, L. A. K. See Davies, T., 2304.
Stephen, A. M. See Lamchen, M., 2429.
Stephen, W. I. See Belcher, R., 2543.
Stephenson, E. F. M., 2354.
Stephenson, R. J. See Shoppee, C. W., 2230.
Stock, J. A. See Bergel, F., 2409.
Stuart-Webb, I. A. See Adams, W. J., 2209, 2298.
Swan, G. A. See Anderson, R. M., 2579.
Tadros, W., Ekladius, L., and Sakla, A. B., 2351.
Tatchell, A. R. See Howard, G. A., 2400.
Taylor, H. T. See Baddeley, G., 2405.
Taylor, W. I., 2636.
Taylor, W. I. See also Little, J. S., 2636.
Tedder, J. M., 2646.
Telfer, R. G. J. See Harwood, V. D., 2364.
Theobald, R. S. See Goldberg, A. A., 2357, 2641.
Thomas, B. R. See Little, J. S., 2636.
Todd, A. R. See Kenner, G. W., 2288, and Lecocq, J., 2381.
Trotman-Dickenson, A. F. See Clark, D., 2633.
Turnbull, J. H., and Wilson, W., 2301.
Turner, E. E. See Hall, D. M., 2498.
Turpin, D. G. See Hey, D. H., 2471.
Vernon, C. A. See de la Mare, P. B. D., 2504.
Vincent, H. C. G., 2423.
Walker, H. A. See Goldberg, A. A., 2540.
Waters, W. A. See Drummond, A. Y., 2456.
Webb, R. F. See Kenner, G. W., 2288.
Webster, W. See Gasson, E. J., 2161, 2170.
Weymouth, F. J. See Kenner, G. W., 2288.
Williamson, W. See Goldberg, A. A., 2357.
White, A. M. See Davies, A. G., 2200.
Whitehouse, M. W., Kent, P. W., and Pasternak, C. A., 2315.
Wild, A. M. See Gasson, E. J., 2170.
Wilson, W. See Turnbull, J. H., 2301.
Woolf, A. A. See Lord, G., 2546.
Wyatt, P. A. H., 2647.
Young, D. P. See Gasson, E. J., 2161, 2170, and Graham, A. R., 2180.

NOTICES TO AUTHORS OF PAPERS

Scientific communications for the *Journal* should be addressed to " The Honorary Secretaries, The Chemical Society, Burlington House, London, W.1." Papers to be read before a meeting of the Society are selected by the Honorary Secretaries.

A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

Communications that have appeared or have been accepted for publication with essentially the same scientific content in another Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

Papers are accepted by the Society on the understanding that the authors have obtained any necessary authority to publish.

The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to withdraw or delay them, or to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references.

Authors are requested to see that their papers conform, as nearly as possible, to the normal conventions of the *Journal*. It is essential that drawings and photographs be presented in the style required by the Society. Every paper must be prefaced by a short summary, but " Notes " do not require a summary. Authors should consult the brochure entitled " The Presentation of Papers for the Journal of the Chemical Society " for detailed instructions and advice on these and cognate matters; Fellows of the Society are entitled to one copy each, gratis, on application to the General Secretary, The Chemical Society, Burlington House, London, W.1; further copies may be obtained at the public price which is 1*s.* 6*d.* each, post free, or 12*s.* 6*d.* per 10 copies, post free.

Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed are reviewed in " Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067) (6*d.* post free), and in the Editorial Reports on Nomenclature (*J.*, 1950, 3699; 1951, 3515; 1952, 5057) (1*s.* each post free). Much valuable discussion will be found in " British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold and Co., 1948]. Authors should choose their symbols from the " Report by the Symbols Committee of the Royal Society representing the Royal Society, the Chemical Society, the Faraday Society, and the Physical Society, 1951 " (*J.*, 1951, 1677) [9*d.* per copy or 12*s.* per 25 copies (post free), obtainable from the General Secretary, The Chemical Society].

Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors.

Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs and the MS. to the Editor.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows paying the Annual Subscription of £4 10*s*. have the following privileges:

To receive a selection of the publications of the Society to a value of £3 0*s*. without further payment.

To purchase additional publications at favourable prices.

To attend all meetings, discussions and lectures of the Society and to introduce two guests.

To consult and borrow books in the Library. Books may be borrowed by post.

To apply for grants from the Research Fund.

To submit papers for publication in the *Journal*.

Fellows under 27 years of age may pay £1 15*s*. per annum and receive:

The *Proceedings*, *Annual Reports on the Progress of Chemistry*, and *Quarterly Reviews* without further payment.

The right to purchase other publications at favourable prices.

All the other privileges of Fellowship.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 50,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London.*—Scientific Meetings of the Society are usually held on two Thursdays in each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London.*—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

A brochure describing the activities of the Society and forms of application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

Oxidation Products of Diisobutylene. Part I. Liquid-phase Oxidation of Diisobutylene: Formation, Properties, and Analysis of 1 : 2-*Epoxy*-2 : 4 : 4-*trimethylpentane.*

By E. J. Gasson, A. F. Millidge, G. R. Primavesi, W. Webster, and D. P. Young.

[Reprint Order No. 4938.]

By oxidising 2 : 4 : 4-trimethylpent-1-ene (α-di*iso*butylene) with air under pressure at 130—140°, up to 56% yields of the derived epoxide (1 : 2-epoxy-2 : 4 : 4-trimethylpentane) are obtained, provided that the reaction medium is kept neutral or slightly alkaline. In the absence of any added base, the epoxide formed in the early stages of the oxidation later disappears, the final products being formic acid, 4 : 4-dimethylpentan-2-one, 2 : 4 : 4-trimethylpentane-1 : 2-diol, etc. These are also obtained as by-products in making the epoxide by the process just outlined. 2 : 4 : 4-Trimethylpent-2-ene (β-di-*iso*butylene) also gives the corresponding epoxide under analogous conditions.

Difficulties have been experienced in applying functional-group analysis to these epoxides, and a new method is proposed.

A number of papers and patents have described the liquid-phase oxidation of olefins by molecular oxygen; a large variety of products has usually been reported, the most usual being carboxylic acids, alcohols, aldehydes, and ketones. There is little doubt that these are end-products of a series of reactions, and some investigators have attempted to arrest the oxidation at an earlier stage.

The autoxidation of commercial di*iso*butylene, a mixture of 2 : 4 : 4-trimethylpent-1-ene (80%) and -2-ene (20%), is mentioned specifically in only four publications. French Pat. 816,055/1937 claims the oxidation in the liquid phase of tertiary olefins with gaseous oxygen or peroxides in the presence of metallic catalysts. The products are stated to be mainly unsaturated alcohols and ketones. Bost (*Science*, 1938, **88**, 440) states that the oxidation of di*iso*butylene by molecular oxygen under pressure at elevated temperatures gave peroxides, aldehydes, ketones, and acids. Di*iso*butylene was also oxidised with oxygen at 100° and 100 lb./sq. in. pressure in the presence of solid potassium hydroxide (Bost and Lockhart, *J. Amer. Chem. Soc.*, 1941, **63**, 2790); qualitative tests on the product showed the presence of methyl ketones, acids, alcohols, and 1 : 2-glycols, and traces of peroxides and aldehydes. The substances specifically identified were acetone, 4 : 4-dimethylpentan-2-one, carbon dioxide, and formic and pivalic acids. In U.S.P. 2,475,605/1949 there is an example showing the oxidation of di*iso*butylene with air at 200 lb./sq. in. at 130—133°: the products are described as the lower oxidation products (alcohols, ethers, ketones, and aldehydes).

The formation of epoxides from autoxidation of olefins has been described by Paquot (Thesis, Paris, 1943) and by Schneider and Sommer (U.S.P. 2,052,195/1936.) This patent describes how, if oxygenation is carried out in presence of mild alkalis, the epoxide is protected against hydrolytic attack and remains in the product. A series of papers by Byers and Hickinbottom (*J.*, 1948, 284, 1328, 1331, 1334) upon the oxidation of di*iso*butylene with chemical reagents describes a number of the compounds that we have encountered.

In the present work, experiments were commenced in glass apparatus with oxygen at atmospheric pressure at 90—95°. Pure freshly distilled 2 : 4 : 4-trimethylpent-1-ene underwent oxidation thus in a typically autocatalytic manner; the oxygen absorption followed a sigmoid curve against time, as shown in Fig. 1*a*, which also shows the concentration of various products (measured by titration) during the experiment. As can be seen, peroxides remained almost constant, at about 2·5—3·5 mol. %, but acids, esters, and carbonyl compounds increased continuously. Considerable quantities of epoxide were detected in the earlier stages, increasing to a maximum of 8 mol. % but thereafter falling to zero. As will be shown later, the amounts of epoxide actually present would be somewhat higher than those found by titration. In presence of 0·1% of cobalt naphthenate, the

concentration of peroxide was much lower throughout, and the oxidation showed no induction period (Fig. 1*b*).

The major components of the final product were formic acid, formates, 4 : 4-dimethylpentan-2-one, 2 : 4 : 4-trimethylpentane-1 : 2-diol, and a high-boiling oil typical of the dimeric condensation products obtained from 1 : 2-epoxy-2 : 4 : 4-trimethylpentane and its derivatives (cf. Part III, *J.*, 1954, 2180). A very similar mixture was obtained from atmospheric oxidation of 2 : 4 : 4-trimethylpent-1-ene (with 10% of the -2-ene) in a stainless-steel pressure vessel at 120° and 200 lb./sq. in. Little hydrocarbon remained; extended fractionation of the product gave 4 : 4-dimethylpentan-2-one (20% of theory), 2 : 4 : 4-trimethylpentane-1 : 2-diol and its formate (5% together), and the other compounds just mentioned.

In view of the potential value of the epoxide, attempts were then made to arrest the course of oxidation at that stage. Oxygenation in presence of bases to neutralise acids as they were formed, so stabilising the epoxide, led to about 50% yields of 1 : 2-epoxy-2 : 4 : 4-trimethyl pentane from commercial di*iso*butylene. Aqueous sodium carbonate was a suitable base, although magnesium oxide or a phosphate buffer could also be used. The oxidation was carried out batchwise by passing air at 200 lb./sq. in. (gauge) into di*iso*butylene at 140° with vigorous stirring, whilst aqueous sodium carbonate was pumped in at such a rate as to maintain the pH of the aqueous layer at 8—8·5. In an adaptation for continuous working, about the same yield of epoxide was obtained.

Small amounts of various metallic compounds, *e.g.*, cobalt, lead, manganese, or iron naphthenates, or sodium vanadate or tungstate, were normally added as initiators. When no initiator was added, the oxidation still appeared to proceed normally, with the yield of epoxide possibly slightly lowered. It is probable, however, that traces of metallic catalysts were always present in the system. There were no notable differences in yield with the various catalysts used, although alkali-soluble catalysts (vanadate and tungstate) gave a cleaner product.

The product was worked up by fractional distillation of the organic phase. Besides 1 : 2-epoxy-2 : 4 : 4-trimethylpentane (40—55% of theory on 2 : 4 : 4-trimethylpent-1-ene consumed) and unchanged hydrocarbon, there were obtained 4 : 4-dimethylpentan-2-one (10% on total di*iso*butylene consumed) and 2 : 3-epoxy-2 : 4 : 4-trimethylpentane (37% on 2 : 4 : 4-trimethylpent-2-ene), mainly together as an azeotrope; also, lower-molecular compounds such as acetone, methacraldehyde, and *tert.*-butanol, and higher-boiling products in which 2 : 4 : 4-trimethylpent-1-en-3-ol, 2-*neo*pentylprop-2-en-1-ol (see Part II, following paper), and 2 : 4 : 4-trimethylpentane-1 : 2-diol were recognised. The aqueous phase contained carboxylic acids, mainly ββ-dimethylbutyric and possibly pivalic and αγγ-trimethylvaleric. A weight balance on one batch experiment, oxidised to 48% conversion of hydrocarbon, was as follows:

Consumed, g.		Produced, g.	
Mixed di*iso*butylene	100	1 : 2-Epoxy-2 : 4 : 4-trimethylpentane	53·5
Oxygen	39	Azeotrope of dimethylpentanone and 2 : 3-epoxy-2 : 4 : 4-trimethylpentane	15·6
		Low-boiling material (mainly *tert.*-butanol)	8·2
		High-boiling material (25% unsaturated alcohols, 20% glycols)	14·5
		Water and acids	19·2
		Carbon dioxide	14·0
		Volatile matter in effluent gas	9·8
		Unaccounted for	4·2
	139		139·0

A similar experiment with purified 2 : 4 : 4-trimethylpent-1-ene (in presence of aqueous disodium hydrogen phosphate as buffer) gave dimethylpentanone (11%), 1 : 2-epoxide (48%), and high-boiling residue (10%). The recovered olefin was substantially free from β-isomer, and no 2 : 3-epoxide was formed; hence no isomerisation occurred during oxidation.

Since the oxidation of di*iso*butylene was not carried to completion, unchanged olefin was

recovered from the product. This could be re-used for fresh oxidations with sodium vanadate catalyst in the normal way. When attempts were made to re-use the recovered olefin with cobalt catalyst at high pH (>7), an unexplained retardation was repeatedly observed after oxidation had proceeded normally for about 1·5 hr. This effect occurred even when the olefin had been carefully washed and fractionated. It could be prevented by lowering the pH to 6—7.

The oxidation of purified 2 : 4 : 4-trimethylpent-2-ene was also investigated. Some small-scale experiments in glass at 90° with oxygen at atmospheric pressure, and in the presence of magnesia, showed that in the absence of a catalyst there was a long induction period, but that addition of a small amount of cobalt naphthenate or benzoyl peroxide initiated an immediate absorption of oxygen. Epoxide was detected in the product, but analytical difficulties (see below) prevented a quantitative assessment. The peroxide-initiated reaction led to more peroxidic products, mainly *tert.*-butyl hydroperoxide, than did oxidation of 2 : 4 : 4-trimethylpent-1-ene.

Oxidation of 2 : 4 : 4-trimethylpent-2-ene under pressure (200 lb./sq. in.) in the stainless-steel vessel at 130—140° (2·5 hr.) in presence of magnesium oxide gave a product in which the following were identified: unchanged 2 : 4 : 4-trimethylpent-2-ene (no -1-ene was detected), (?) *iso*butaldehyde, *tert.*-butanol, 4 : 4-dimethylpentan-2-one, 2 : 3-epoxy-2 : 4 : 4-trimethylpentane (25—26% yield), 2 : 4 : 4-trimethylpent-1-en-3-ol, and higher-boiling material probably containing diketones and 2 : 4 : 4-trimethylpentane-2 : 3-diol. By treatment with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid, a red derivative, m. p. 202—203°, was obtained from one of the higher fractions: this was identical with 2 : 4 : 4-trimethylpent-2-en-1-al 2 : 4-dinitrophenylhydrazone (Hadley, Hall, Heap, and Jacobs, *J.*, 1954, 1416), and it is probably also identical with Hickinbottom's presumed *tert.*-butylpyrazoline (*J.*, 1949, 287). The nature of the high-boiling product giving rise to this unsaturated hydrazone is uncertain; it may be 1 : 2-epoxy-2 : 4 : 4-trimethylpentan-3-ol (II), as a possible precursor (2 : 4 : 4-trimethylpent-1-en-3-ol; I) of this is present in the oxidate:

$$\underset{\text{(I)}}{HO\cdot CHBu^t\cdot CMe{:}CH_2} \longrightarrow \underset{\text{(II)}}{HO\cdot CHBu^t\cdot \overset{O}{\overset{\diagdown\diagup}{C}}Me\cdot CH_2} \longrightarrow \underset{\text{(III)}}{CHBu^t{:}CMe\cdot CH{:}N\cdot NH\cdot C_6H_3(NO_2)_2}$$

A subsequent oxygenation under similar conditions, but with sodium vanadate catalyst and aqueous sodium carbonate as base, gave a 53% yield of the isolated 2 : 3-epoxide.

Analysis of the Epoxides.—The epoxides were purified by further fractionation, and a sample of 1 : 2-epoxide obtained by this means was shown by freezing-point observations to be over 99·5% pure. Unexpected difficulty was encountered in assaying the purity of these epoxides by functional-group analysis by any of the conventional procedures. For example, Nicolet and Poulter's method (*J. Amer. Chem. Soc.*, 1930, **52**, 1186; Swern *et al.*, *Anal. Chem.*, 1947, **19**, 414) using hydrogen chloride in ether, applied without special precautions, gave only 79% of the expected titration on a pure sample. Furthermore, when applied to mixed products it gave unreproducible results. When this work was started, no cases of failure of the method had been recorded, although Hickinbottom and Wood (*J.*, 1951, 1601) have since reported that 1 : 2-epoxy-4 : 4-dimethyl-2-*neo*pentylpentane gives no titration at all.

Since a reliable quantitative method was desirable, Nicolet and Poulter's method as applied to the 1 : 2-epoxide was further investigated. It was found that factors such as the concentration of the sodium hydroxide used for titration, the freshness of the ether, and the order of mixing reagents all affected the result. The procedure was therefore modified (see p. 2168), and, if rigidly adhered to, it could then give 95% of the expected figure.

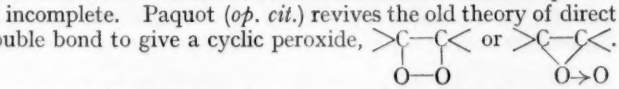
Various other published procedures for estimating epoxides, such as those based on interaction with magnesium chloride (Lubatti, *J. Soc. Chem. Ind.*, 1932, **51**, 361T), hydrochloric acid in dioxan (King, *Nature*, 1949, **164**, 706), or sodium thiosulphate (Ross, *J.*, 1950, 2270), gave valueless results. Oxidation with periodic acid gave a very approximate estimate (10% low), although sodium periodate (cf. Hirst and Jones, *J.*, 1949, 1659), either in aqueous or in *iso*propanol solution, gave quite unreproducible results.

The failure of these methods is understandable in view of the ready isomerisation of the 1 : 2-epoxide, especially in acid medium. An examination of the products of interaction of the 1 : 2-epoxide with hydrogen chloride (Part III, *loc. cit.*, p. 2186) showed that, besides the chlorohydrin, trimethylpentanal was formed, and further that the chlorohydrin readily lost hydrogen chloride.

An analytical method was finally developed based on reaction of the epoxide with dibutylamine. This gave results closely agreeing with the value expected from physical methods, although reproducibility was not high (standard error for a single determination up to 1·3%), and the procedure was too lengthy for a routine method.

No satisfactory chemical method for estimating the 2 : 3-epoxide was found at all, as it gave only a fraction of the expected titration by any of the methods mentioned (the dibutylamine method was not tried).

Once a pure reference sample was obtained, fairly pure samples of the 1 : 2- or 2 : 3-epoxides could be assayed by infra-red spectroscopy, but the absence of any strong absorption bands precluded the spectroscopic estimation of epoxides in mixed products. All yields quoted in this paper, unless otherwise stated, refer to isolated material corrected for impurity by spectroscopic measurement.

Mechanism of Epoxidation.—We have not been able to obtain any direct evidence as to the mechanism of this interesting reaction. Current theory of autoxidation postulates that the initial attack consists of the removal of the least strongly bound hydrogen atom. On this basis, attack at the 3-position in the 2 : 4 : 4-trimethylpent-1-ene molecule would be expected, but in fact very little product that is unequivocally formed by this route has been obtained. Since over 50% yields of epoxide can be isolated, and much of the residual product (diol, dimeric condensation products, and probably dimethylpentanone) appears to be derived from epoxide which has undergone further reaction, any mechanism based on initial formation of a 3-hydroperoxide which later oxidises a further molecule of olefin to epoxide is unlikely or at least will be incomplete. Paquot (*op. cit.*) revives the old theory of direct addition of oxygen to the double bond to give a cyclic peroxide,  or .

Although the existence of such peroxides has never been proved, it is difficult to escape the conclusion that in the present case the initial attack upon the olefin is mainly at the double bond. On this view, the unsaturated alcohols in which a hydroxyl group has entered at the 1- or the 3-position are the products of side-reactions. A parallel may be drawn with the action of chromium trioxide in acetic anhydride, which normally attacks the carbon atom in the allyl position (Treibs and Schmidt, *Ber.*, 1928, **61**, 459), but with 2 : 4 : 4-trimethylpent-1-ene yields the epoxide as main product (Byers and Hickinbottom, *J.*, 1948, 1334; cf. also Hickinbottom and Wood, *loc. cit.*).

The oxidation herein described has characteristics (autocatalytic and inhibition effects) of a radical-chain reaction, and on this basis may be presumed to be homopolar. This is in contrast to epoxidation by means of peracids, which shows normal kinetics and appears to be heteropolar (Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692). Here again the precise mechanism is still uncertain, the most plausible explanation being that advanced by Criegee (*Fortschr. Chem. Forsch.*, 1950, **1**, 550), envisaging addition of a hydroxyl cation followed by elimination of a proton.

Experimental

Materials.—The di*iso*butylene used was mainly the equilibrium mixture of isomers [80% of 2 : 4 : 4-trimethylpent-1-ene (" α "), 20% of -2-ene (" β ")], but a few experiments were carried out with material enriched in the α-isomer by fractional distillation, and also on the pure isomers.

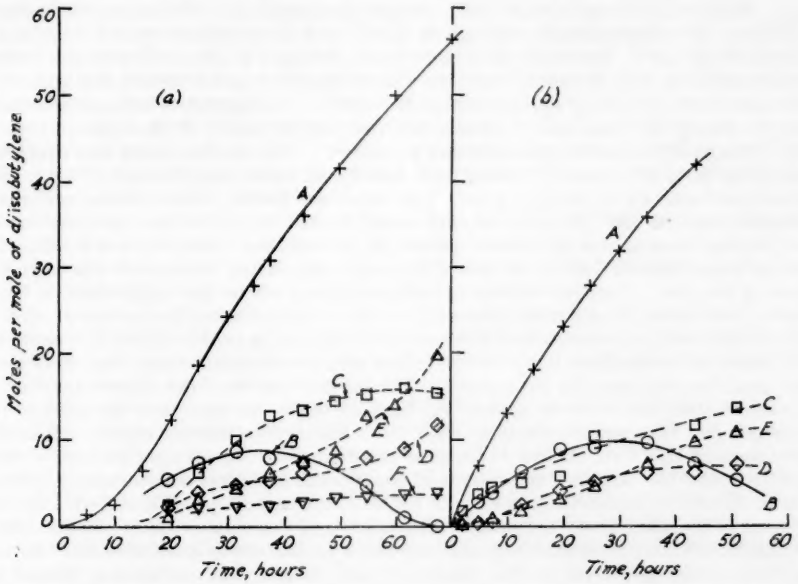
The commercial olefin was obtained from two sources, (i) a crude polymerisate from Anglo-Iranian Oil Co. Ltd., from which di*iso*butylene was separated by distillation, (ii) a purified di*iso*-butylene, of U.S. origin, substantially free from other hydrocarbons but containing an oxidation inhibitor. In order to obtain consistent results it was necessary to distil the latter material before use.

With few exceptions, the oxidations were catalysed by heavy-metal salts, added as the oil-

soluble naphthenates (" Novenates "; A. Boake Roberts & Co.), normally at 0·1% w/v on the olefin.

Oxidation of 2 : 4 : 4-*Trimethylpent*-1-*ene in Glass Apparatus with Oxygen at Atmospheric Pressure.*—Freshly distilled 2 : 4 : 4-trimethylpent-1-ene (213 g.) was agitated in oxygen, by means of a " recycle " stirrer, in a flask immersed in a bath at 90—95°. Samples were withdrawn at 6-hourly intervals for titration. The progress of the experiments is summarised in Figs. 1*a* and 1*b*. Distillation of the final oxidate gave formic acid, water, formic esters, 4 : 4-dimethylpentan-2-one, b. p. 70°/150 mm. (semicarbazone, m. p. 176°, undepressed by an authentic specimen), 2 : 4 : 4-trimethylpentane-1 : 2-diol, m. p. 62—63° (not depressed by an authentic specimen), and a substance, b. p. 66—67°/2 mm., n_D^{20} 1·4438, *M* (in camphor) 251, which was apparently a bimolecular condensation product of the epoxide (cf. Hickinbottom, *J.*, 1948, 1328, 1331, and Part III).

FIG. 1. *Oxidation of* 2 : 4 : 4-*trimethylpent*-1-*ene at atmospheric pressure in absence of alkali,* (*a*) *without catalyst,* (*b*) *with* 0·1% *of cobalt naphthenate. A, oxygen absorbed; B, epoxide formed; C, carbonyl compounds formed; D, acids formed; E, esters formed; F, peroxides formed.*



Oxidation of Diisobutylene in a Steel Vessel with Air under Pressure.—Apparatus. The reaction vessel and its fittings were constructed of FDP stainless steel. The vessel consisted of a cylinder, 10 cm. in diameter and about 30 cm. long. with flanged ends, with a total capacity of *ca.* 2·1 l. It was heated electrically by a winding carrying 5 amp. at 230 v, and was equipped with a Kestner turbo-type stirrer, 5 cm. in diameter, rotating at *ca.* 1400 r.p.m. Through the bottom flange passed pipes for the air supply (immediately under the stirrer), and for the withdrawal and sampling of the product. Through the top flange passed the gas exit line, the reflux return line, and a thermometer pocket. The air was supplied from storage tanks at 300 lb./sq. in., and the pressure in the reaction vessel was kept constant by means of a reducing valve on the inlet side; air flow *into* the vessel was not measured. The exit gases passed down a water-cooled coil condenser, and then through a gas–liquid separator, the liquid reflux being returned to the vessel through a U-bend. The gases passed on and were reduced to atmospheric pressure through a hand-controlled needle-valve, kept warm to avoid condensation and freezing-up; the rate of flow through the apparatus was controlled entirely by this valve. The gas at atmospheric pressure was passed through a capillary flowmeter and wet gas-meter, but in advance of the flowmeter a very small proportion of the gas was drawn off to an oxygen meter. The alkali solution was pumped into the vessel from a measuring tank *via* an entry into the reflux-return line at the top of one arm of the U. The vessel was charged through the thermometer pocket.

Catalysed oxidation in absence of alkali. Di*iso*butylene (1070 g., 9·5 moles; containing *ca.* 90% of α-isomer) containing 0·1% of cobalt naphthenate was oxidised with air at *ca.* 120° and under 200 lb./sq. in. pressure. The air rate was such that the effluent gas rate was 120 l./hr., the oxygen being completely absorbed. About 12—14 moles of oxygen were absorbed during 14·5 hr. The product (1224 g.) was extracted with aqueous sodium carbonate, and this was extracted with 200 ml. of di*iso*butylene, which was added to the acid-free oxidate. This was then distilled, leaving some 4—5% of tarry residue. The fractions, b. p. 80—94°/6—7 mm., deposited 65 g. of 2 : 4 : 4-trimethylpentane-1 : 2-diol, m. p. 61° after recrystallisation. The liquid portion of the distillates was refractionated to give (percentages are of crude product): (i) b. p. 52—67° (1·1%; acetone and some formaldehyde), (ii) 67—80° (1·6%), (iii) 80—85° (3·3%; *tert.*-butanol), (iv) 85—120° (16%; di*iso*butylene and water), (v) 120—130° (18·5%; 4 : 4-dimethylpentan-1-one), (vi) 130°/760—101°/14 mm. (14·55%), (vii) 101—102°/14 mm. (2·75%), (viii) 102—116°/14 mm. (7·1%). Fraction (iv) was equivalent to the di*iso*butylene used for extraction, and hence the amount of olefin unchanged from the oxidation was nil. Fraction (vii) was about 65% of 2 : 4 : 4-trimethylpentane-1 : 2-diol formate; from it were obtained by hydrolysis with alcoholic potash a further 12·2 g. of the free diol, and potassium formate. Fraction (viii) was mainly cyclic condensation product. With an alcoholic sulphuric acid solution of dinitrophenylhydrazine it gave 2 : 4 : 4-trimethylpentanal dinitrophenylhydrazone, m. p. 163°. The major single compound obtained in this oxidation was trimethylpentanone (yield *ca.* 20% of theory), and the total yield of free and esterified diol was 5%.

Oxidation in the presence of aqueous sodium carbonate. The solution of sodium carbonate was pumped in during the oxidation at such a rate that the pH limits of the aqueous layer were 7—8·5. Details of a typical experiment are as follows. The reaction vessel was charged with di*iso*butylene (80% of α-isomer; 1075 g., 9·6 moles) and cobalt naphthenate (1·5 g.), and the pressure raised with air to 100 lb./sq. in. The vessel was heated, with stirring, and when the temperature reached 130° the pressure was raised to 200 lb./sq. in. and the exit valve was opened slightly so as to give an effluent gas rate of 50—60 l./hr. Heating was continued until the temperature reached 140° (a further 5 min. approximately), whereat it was kept for the duration of the run. Once the oxidation was proceeding, no further application of heat was necessary, and indeed it was often necessary to apply slight cooling (by means of an air-jet). The alkali feed (16% aqueous sodium carbonate) was started, at *ca.* 70—75 ml./hr., about 5 min. after the start of the air flow, but if the oxidation was slow in commencing, the alkali feed was stopped again so as to keep the pH below 9. The oxygen content of the effluent gas dropped as absorption started, and when it reached 5% (usually in 10—30 min. after the start of the air flow) the effluent rate was increased to 180 l./hr. The oxygen content rapidly fell to 0—1% and remained at this level for the duration of the oxidation. Small samples were withdrawn frequently (every 15—30 min.), and the pH of the aqueous layer was determined by spotting on a tile with B.D.H. Universal Indicator. The pH was kept as far as possible at 8—8·5 by suitable adjustment of the alkali feed; normally it settled down at this value without any difficulty, and it was only at the start of an oxidation that any wider variation was liable to occur. After 4 hr. the inlet and outlet gas valves and the alkali feed were closed. The oxidate was allowed to cool to 40° before being discharged from the vessel, or else was passed out through a water-cooled condenser. The product formed a dark brown aqueous layer and a yellow-to-orange upper layer. There was a small amount of dark interfacial sludge (less when sodium vanadate catalyst was used), but the separation of the phases was quite clean.

290 ml. of alkali (equivalent to 53 g. of sodium carbonate) were used. The effluent gas totalled 770 l., and the oxygen absorbed was estimated to be 180 l. (5·2 moles). The product consisted of 990 g. of organic and 407 g. of aqueous phase, hence the aqueous layer had increased in weight by 70 g.

Distillation of the organic phase through an insulated column, 50 × 2·5 cm. (internal), packed with glass helices, at a reflux ratio of 10 : 1, gave (i) b. p. up to 65°/125 mm. (450 g.), (ii) 65°/125—70°/100 mm. (112 g.), (iii) 70—77°/100 mm. (332 g.), and residue (66 g.). Fraction (i), plus the contents of the cold-trap, was washed thrice with water, to give 419 g. of substantially unchanged di*iso*butylene. The olefin consumed was therefore 656 g., so that conversion was 61%. Fraction (iii) was 90—95% 1 : 2-epoxy-2 : 4 : 4-trimethylpentane, so the yield of epoxide was 50—53% on olefin consumed.

The oxidation time was reduced progressively to 2 hr., without appreciably affecting the degree of conversion, by increasing the effluent gas rate (finally to 360 l./hr.), the alkali feed being increased correspondingly. The oxidation proceeded smoothly, and the yields of 1 : 2-epoxide fraction did not alter.

Oxidations were carried out in presence of 0·1—1·0% (overall) of cobalt, manganese, lead, or ferric naphthenate, or sodium vanadate or tungstate dissolved in the alkali feed; in all cases the yield was 51—56% of 1 : 2-epoxide (based on olefin consumed). When no catalyst was added, the vessel (but not the rest of the apparatus) having previously been thoroughly washed out, the yield was 50%.

Some 25% of the distillation residue from the epoxide was composed of unsaturated alcohols. The 2 : 4-dinitrobenzoates of 2 : 4 : 4-trimethylpent-1-en-3-ol (m. p. 118°) and 2-*neo*pentylprop-2-en-1-ol (m. p. 54·5°; cf. Part II, p. 2176) were obtained from fractions of b. p. up to 82°/19 mm. In addition, periodate analysis showed the presence of approximately 20% of glycols, presumably mainly 2 : 4 : 4-trimethylpentane-1 : 2-diol.

The acidic products obtained in the presence of alkali appeared to be similar to those obtained in its absence. Acidification of 10 l. of the alkaline aqueous layer from several oxidations, followed by steam-distillation, gave only about 50 g. of water-insoluble mixed carboxylic acids, b. p. *ca.* 150—220°. The main component seemed to be ββ-dimethylbutyric acid, but from the b. p. it was probable that smaller amounts of pivalic and αγγ-trimethylvaleric acids were also present. The steam-distillate contained in addition 26·5 g. of water-soluble aicds (calculated as formic).

Similar results were obtained by oxidation in presence of magnesium oxide, added to the charge (50 g. to 1075 g. of olefin) either dry or suspended in water. Disodium hydrogen phosphate alone was insufficient to maintain the pH unless sodium hydroxide was pumped in during the oxidation. In this way, 1040 g. of purified α-isomer (more than 99% of 2 : 4 : 4-trimethylpent-1-ene), 1·5 g. of cobalt naphthenate, and 25 g. of $Na_2HPO_4,12H_2O$ in 100 ml. of water, subsequently kept at pH 8—8·5, yielded unchanged hydrocarbon (39·2%), 4 : 4-dimethylpentan-2-one (10% yield on olefin consumed), 1 : 2-epoxide (48%), and residue (10 wt. %). Less than 0·2% of 2 : 3-epoxide was detected.

An oxidation in presence of solid potassium hydroxide (cf. Bost and Lockhart, *loc. cit.*) gave neither epoxide nor carbonyl compounds detectable by analysis.

Later, oxidations were carried out on a larger scale in a 27-l. mild-steel vessel; induction periods and oxidation rates were less reproducible in this apparatus.

Oxidation of 2 : 4 : 4-*Trimethylpent-2-ene.*—Preliminary experiments were carried out in glass apparatus as described above. The peroxidic product was shown (G. W. Godin and J. L. Benton, unpublished work in these laboratories) to be mainly *tert.*-butyl hydroperoxide, isolated through the sodium salt and identified by infra-red spectrum.

Later experiments were carried out in the stainless-steel vessel as described above.

(*a*) 2 : 4 : 4-Trimethylpent-2-ene (911 g., 8·13 moles), magnesium oxide (35 g.), and cobalt naphthenate (1·5 g.) were oxygenated with air at 130—140° for 1·5 hr. [about 4·3 moles of oxygen (137 g.) had been introduced]. 947 G. of product (including magnesia) were recovered, therefore 136 g. had been lost as carbon dioxide and volatiles. After filtration, 730 g. of liquid product were obtained. Titration at this point showed peroxides less than 0·6% (as Bu^tO_2H). It was distilled through a 75-cm. column packed with glass helices to give the following fractions :

Fraction	B. p./mm.	Weight, g.	n_D^{20}	Composition
(i)	55—58°/758	12·0	1·3732	Acetone, etc.
(ii)	58—65°/758	8·5	1·3805	Acetone, (?)*iso*butaldehyde, etc.
(iii)	65—76°/758	19·3	1·3966 *	*iso*Butaldehyde, etc.
(iv)	76—85°/758	65·8	1·3942	Mainly *tert.*-butanol
(v)	85—102°/758	18·0	1·4038	
(vi)	102—103°/758	12·0	1·4127	Unchanged olefin
(vii)	53—58·5°/129	245·0	1·4154	do.
(viii)	58·5—72°/129	17·0	1·4119	Olefin, epoxide (50%), dimethylpentanone
(ix)	72—73°/129	174·0	1·4081	2 : 3-Epoxide (95%)
(x)	58·5—60°/28	23·0	1·4189	2 : 3-Epoxide (30%)
(xi)	60—82°/19	22·5	1·4362	2 : 4 : 4-Trimethylpent-1-en-3-ol, 1 : 2-epoxy-2 : 4 : 4-trimethylpentan-3-ol (or 2 : 4 : 4-trimethylpent-2-enal), diketone, diol, etc.
(xii)	82—96°/19	18·5	1·4369	
(xiii)	96—110°/19	16·5	1·4425	
	Residue	45·5	—	

* Two-phase azeotrope; only upper layer examined.

Acetone was identified in fractions (i) and (ii) by its dinitrophenylhydrazone. Both these fractions also contained a small amount of unidentified material insoluble in water. The evidence for *iso*butaldehyde in fractions (ii) and (iii) is not conclusive; dinitrophenylhydrazones were obtained from both which, after repeated recrystallisations from alcohol, melted at 180—

182° with previous softening below 170°; a mixed m. p. with the derivative of *iso*butaldehyde gave no depression of the final m. p. *tert.*-Butanol was identified as its phenylurethane. Infra-red examination showed that no isomer of 2 : 4 : 4-trimethylpent-2-ene was present in fractions (vi) and (vii), but they contained traces of ketones and alcohols. From fraction (viii) some 4 : 4-dimethylpentan-2-one was isolated as its dinitrophenylhydrazone. Fraction (xi) gave reactions for both carbonyl and hydroxyl. With alcoholic 2 : 4-dinitrophenylhydrazine containing sulphuric acid it gave a red derivative, m. p. 202—203° after recrystallisation. This was identical (mixed m. p.) with a sample of 2 : 4 : 4-trimethylpent-2-en-1-al dinitrophenylhydrazone (III) (Hadley *et al., loc. cit.*). Fraction (xi) also gave a 3 : 5-dinitrobenzoate, which appeared to be a mixture. After repeated recrystallisation, its m. p. had risen from 62—66° to 108—110°, and the purified derivative gave no depression of m. p. in admixture with that of 2 : 4 : 4-trimethylpent-1-en-3-ol. From other higher fractions were isolated a dinitrobenzoate, m. p. 79—81°, apparently the impure bisdinitrobenzoate of a C_8 diol, and a dinitrophenylhydrazone, m. p. 254—256°, of analytical composition approximately that of the bisdinitrophenylhydrazone of a C_8 diketone. Besides the compounds already mentioned, there was evidence from titrations of small amounts of glycols and esters.

(*b*) 2 : 4 : 4-Trimethylpent-2-ene (1080 g.) was oxygenated at 140° with air at 200 lb./sq. in. for 2·5 hr. Meanwhile 15% sodium carbonate solution in which was dissolved 1·0% of vanadium pentoxide was pumped in to keep the pH at 8—9; 500 ml. in all were used. The effluent gas emerged at 300 l./hr., all oxygen having been absorbed. The oil phase of the product was distilled, and the fraction, b. p. 60—70°/100 mm. (46·9%; 53·5 wt. % of the olefin consumed), was estimated by infra-red measurements to be 100% pure 2 : 3-epoxy-2 : 4 : 4-trimethylpentane.

Properties of the Diisobutylene Oxides.—A redistilled sample of 1 : 2-epoxy-2 : 4 : 4-trimethylpentane, b. p. 75°/93 mm., n_D^{20} 1·4155, was estimated by f. p. to be 99·5% pure. 2 : 3-Epoxy-2 : 4 : 4-trimethylpentane, b. p. 66°/100 mm., n_D^{20} 1·4078, was similarly found to be 98% pure.

The following vapour-pressure data were observed :

Vapour pressure, mm.	49	50	73	74	99	100	150	200
	Temperature							
1 : 2-Epoxy-2 : 4 : 4-trimethylpentane	—	61·6°	—	70·4°	—	77·4°	98·7°	95·5°
4 : 4-Dimethylpentan-2-one	49·2°	—	57·9°	—	65·0°	—	—	83·0
Azeotrope of dimethylpentanone and 2 : 3-epoxide	—	49·8	58·0	—	65·2	—	75·0	83·0

It appears that the dimethylpentanone was slightly impure, and its true b. p. is slightly higher than that of the azeotrope.

Fractions containing the two epoxides and 4 : 4-dimethylpentan-2-one were estimated by infra-red spectroscopy by the method of matching mixtures, in order to obviate the small error caused by the overlapping of bands. Maxima at 883 and 901 cm.$^{-1}$ were found to be characteristic of 1 : 2- and 2 : 3-epoxy-2 : 4 : 4-trimethylpentane respectively, and further maxima at 958 and 1253 cm.$^{-1}$ provided key points for the matching. The ketone can be matched by a band at 1151 cm.$^{-1}$, although the carbonyl absorption gives a more sensitive test for its presence. The absorption curves of the two epoxides are shown in Fig. 2.

Functional-group Analysis of 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane.—Ethereal hydrogen chloride method. A statistically-planned investigation of the method (Swern *et al., loc. cit.*) showed that the following factors all had a significant effect on the result : molar ratio hydrogen chloride : epoxide, dilution of the sample before addition, and order of addition of the reagents, the first two not being independent. The amount of agitation during mixing, and increasing the time of reaction from 30 to 90 min., made no significant difference. Diluting the blank (*i.e.*, reagents without epoxide sample) with ether increased the titration by an amount depending on the order of addition.

The following procedure, rigidly followed, gave a mean result of 94·25% of the true amount, with a standard error for a single determination of 0·53%. To 10 ml. of approx. 0·6N-hydrogen chloride in ether in an iodine flask was added with swirling a solution of about 0·4 g. of epoxide in 10 ml. of ether. This was set aside, stoppered, for 30 min. Then 30 ml. of 0·015% alcoholic α-naphtholphthalein were added, and the contents were titrated with 0·2N-sodium hydroxide to an end-point not fading in 15 sec. A blank determination was carried out in exactly the same way, but with omission of the epoxide.

Blank titrations on the same materials drifted with time, apparently depending on fluctuations in the ambient temperature. Hence it would be better to run blanks simultaneously with

each sample. The presence of 0·5% of sulphuric acid in the reagent (this is 31% of the hydrogen chloride content) caused results to be 13% lower than otherwise.

Periodate method. The method described in *J.*, 1949, 2998 (*Note :* " iodate " is a misprint for " periodate ") was applied, by shaking the sample with the acid periodate in a stoppered flask for 30 min. Pure 1 : 2-epoxide had an apparent purity of 90% by this method.

Dibutylamine method. About 0·2 g. of epoxide was weighed into a clean, dry, glass tube of about 6 mm. internal diameter, 30 cm. long, and 1 mm. wall thickness, closed at one end. It was washed in with 1·25 ml. of methanol, and 0·5 ml. of di-*n*-butylamine and 0·4 ml. of water (all fairly accurately measured) added. The tube was sealed, the contents mixed, and the tube heated for 2 hr. in a steam pressure-vessel at 200 lb./sq. in. After cooling, the tube was opened and the contents were poured into a test-tube and washed in with 10 ml. of acetic anhydride in

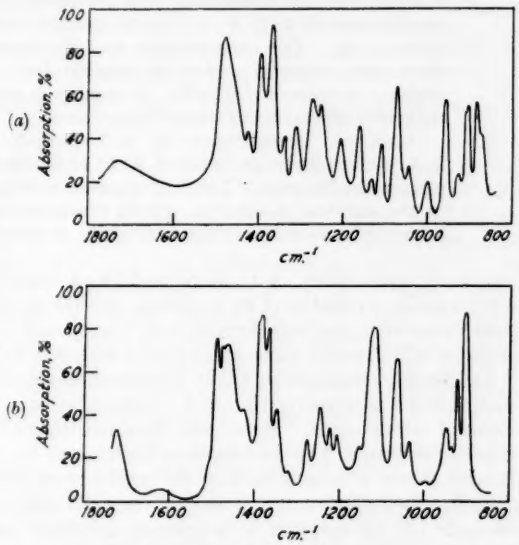


FIG. 2. *Infra-red absorption spectra of* (*a*) 1 : 2-*epoxy*-2 : 4 : 4-*trimethylpentane*, (*b*) 2 : 3-*epoxy*-2 : 4 : 4-*trimethylpentane*.

several portions. After mixing, the solution was heated at 55° for 1·5 hr. with exclusion of moisture. A blank determination was run, the epoxide being omitted. At this point, 10 ml. of acetic acid were added to the blank only. After addition of one drop of 0·5% metanil-yellow in acetic anhydride containing 2% of acetic acid, the blank was titrated with 0·1N-perchloric acid in acetic acid until the colour was just changing from reddish-brown to purple. This titration should not exceed 0·2 ml. The sample was then similarly titrated to match the blank, and the difference between the two titrations was the equivalent of the *tert.*-amine formed and hence of the epoxide.

A sample analysed thus gave 100·35% of epoxide, as the mean of 24 results, with a standard error of a single determination of 1·31%. The same sample analysed by f. p.-measurement was found to be 99·0 ± 0·5 mol. % pure.

We are indebted to Mr. H. C. Highet for fractionating the starting material and for the vapour-pressure data; to Mr. D. R. Read for the statistical design and interpretation of the analytical results; and to Mr. A. R. Philpotts for spectroscopic and freezing-point determinations. We also thank the Directors of The Distillers Company Ltd. for permission to publish this paper.

THE DISTILLERS COMPANY LIMITED, RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM, SURREY. [*Received, December 29th*, 1953.]

Oxidation Products of Diisobutylene. Part II. The Isomerisation of 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane, and Some Products derived from 2 : 4 : 4-Trimethylpentanal.*

By E. J. Gasson, A. R. Graham, A. F. Millidge, I. K. M. Robson, W. Webster, A. M. Wild, and D. P. Young.

[Reprint Order No. 4939.]

The catalytic isomerisation of 1 : 2-epoxy-2 : 4 : 4-trimethylpentane to 2 : 4 : 4-trimethylpentanal has been studied, in the liquid and in the gas phase, and optimum conditions have been determined. The trimethylpentanal can be readily reduced to 2 : 4 : 4-trimethylpentan-1-ol or oxidised to αγγ-trimethylvaleric acid. The isomerisation and hydrogenation can be carried out on the crude oxidation product of di*iso*butylene without isolation of the intermediate epoxide or aldehyde. A number of amines have been prepared from reductive amination of trimethylpentanal.

Catalytic isomerisation of 2 : 3-epoxy-2 : 4 : 4-trimethylpentane yields 2 : 4 : 4-trimethylpent-1-en-3-ol, 2 : 4 : 4-trimethylpentan-3-one, and 2 : 2 : 3 : 3-tetramethylbutanal. The 1 : 2-epoxide undergoes isomerisation when heated in the absence of catalyst, giving 2-*neo*pentylprop-2-en-1-ol; some 2 : 4 : 4-trimethylpentan-2-ol is also formed by an unknown mechanism.

The ready availability of 1 : 2-epoxy-2 : 4 : 4-trimethylpentane (see preceding paper) led us to examine a number of its reactions and the products derived therefrom. The present paper deals with products derived from the epoxide by prototropic change, and the following paper will describe those arising from ring-opening without isomerisation.

Catalysed Isomerisation of the Epoxytrimethylpentanes.—The literature gives numerous examples of the isomerisation of 1 : 2-epoxides to aldehydes in the liquid phase under the action of strong acids. Byers and Hickinbottom (*J.*, 1948, 1329, 1331) obtained 2 : 4 : 4-trimethylpentanal 2 : 4-dinitrophenylhydrazone by warming 1 : 2-epoxytrimethylpentane (I) with dilute sulphuric acid in the presence of dinitrophenylhydrazine. In the absence of dinitrophenylhydrazine, however, they obtained no more than a 24% yield of the free aldehyde (II) by reaction with aqueous sulphuric acid, the main products being the 1 : 2-diol and a bimolecular condensation product.

We have found that the aldehyde (II) can be obtained in yields of up to 95% under suitable conditions, by isomerisation with sulphuric acid. The principal requirements for optimum yields were the presence of an inert diluent to protect the aldehyde against the strong acid, and rapid isomerisation to reduce the chance of aldehyde–epoxide interaction. Sulphuric acid (50% v/v) was the most suitable catalyst. In more dilute acid (2N), formation of condensation product (cf. *idem, ibid.*) can largely be avoided by minimising the interaction of epoxide with aldehyde. This can best be done by ensuring a rapid reaction by agitation during the addition of epoxide to the acid, by protection of the aldehyde with an inert solvent, and by continuous steam-distillation of the product.

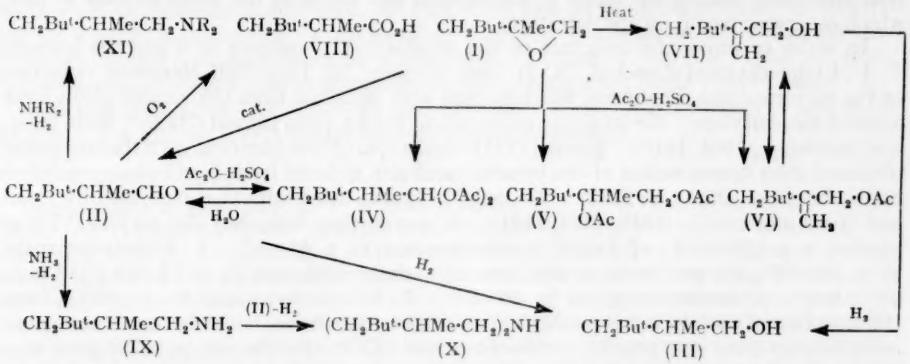
Other efficient liquid-phase catalysts were syrupy phosphoric acid and solid ferric and zinc chlorides. Numerous other catalysts (see Experimental) gave some isomerisation, but yields were poor.

In the vapour phase, the 1 : 2-epoxide isomerised readily at 200—350° over alumina, fuller's earth, or phosphoric acid on an inert support, giving good yields of trimethylpentanal. A " mixed-phase " technique was also tried, the catalyst being suspended in a hot inert solvent whilst epoxide vapour was passed through. However, at contact times sufficiently long to give complete conversion, the yield of aldehyde was lowered and side-reactions increased.

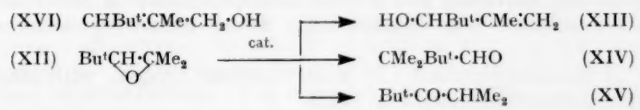
Isomerisation was also observed when the epoxide was added to acetic anhydride containing a trace of sulphuric acid. The expected glycol diacetate (V) was only detected

* Part I, preceding paper.

in very small amount; the major product was the isomeric aldehyde diacetate (IV)—identified by hydrolysis and synthesis—along with some 2-*neo*pentylallyl acetate (VI).



Isomerisation of purified 2 : 3-epoxy-2 : 4 : 4-trimethylpentane (XII) in the liquid phase with dilute sulphuric acid gave mainly 2 : 4 : 4-trimethylpent-1-en-3-ol (XIII) accompanied by 2 : 4 : 4-trimethylpentan-2 : 3-diol, in agreement with Hickinbottom (*ibid.*, p. 1331), who also found 2 : 2 : 3 : 3-tetramethylbutanal (XIV). In our experiment the only identified carbonyl product was 2 : 2 : 4-trimethylpentan-3-one (XV). From isomerisation in the vapour phase over alumina at 279—290°, the product was predominantly the ketone (XV), although a similar experiment with crude 2 : 3-epoxide (available in larger quantities) afforded a small amount of the aldehyde (XIV) as well. The 2 : 4-dinitrophenylhydrazones of these two products have the same m. p. (163°), but, as described by Byers and Hickinbottom, the derivative of (XV) forms orange leaflets and that of (XIV) yellow needles; the m. p. of an admixture is lower than that of either compound.



Non-catalytic Isomerisation of 1 : 2-*Epoxy*-2 : 4 : 4-*trimethylpentane to* 2-neo*Pentylprop*-2-*en*-1-*ol*.—During attempts to make the 1 : 2-epoxide react with an alcohol in absence of catalyst (cf. Part III, p. 2183), small amounts of a product finally identified as 2-*neo*pentylprop-2-en-1-ol (VII) were isolated when a solution of the epoxide in ethanol was heated for a long time at 200° or above. It appeared unlikely that this was derived from either of the ethoxytrimethylpentanols, and experiments confirmed that these were stable under the conditions of experiment, as was 2 : 4 : 4-trimethylpentane-1 : 2-diol. This left the possibility that it was a direct rearrangement product of the epoxide.

Isomerisation of epoxides to aldehydes or ketones by heat is known, especially in the aromatic series (see, *e.g.*, Tiffeneau *et al.*, *Bull. Soc. chim.*, 1931, **49**, 1709). Isomerisation to unsaturated alcohols by means of special catalysts has been described in patents (Fowler and Fitzpatrick, U.S.P. 2,426,264/1947; Lundsted, Schwoegler, and Jacobs, U.S.P. 2,479,632/1949).

When heated above 200° alone in a sealed tube, the epoxide did indeed give some *neo*pentylpropenol (VII). However, more drastic conditions of temperature or time led to formation of a more complex product, in which 2 : 4 : 4-trimethylpentan-1-ol (III) was found; the high unsaturation values sometimes obtained suggested also the presence of a diene, and much higher-boiling material was formed. Heating the epoxide in an inert solvent (medicinal paraffin) also gave only the trimethylpentanol (III) as identifiable product (small yield), and no unsaturated compounds at all.

The saturated alcohol (III) is presumably formed by a dehydrogenation or dispropor-

tionation, so that it should be accompanied by the equivalent amount of a more highly oxidised compound. It is possible that (VII) and (III) are formed simultaneously, but that after long heating the latter is decomposed and unmasks the small amount of (III) which otherwise would escape detection.

In order to prove the structure of the alcohol (VII), samples of it and the isomeric 2 : 4 : 4-trimethylpent-2-en-1-ol (XVI) were prepared by Ponndorff–Meerwein reduction of the corresponding aldehydes, which in turn were obtained from the vapour-phase oxidation of di*iso*butylene; the structure of the aldehydes has been proved (Hadley, Hall, Heap, and Jacobs, *J.*, 1954, 1416). Alcohol (VII) thus prepared was identical with the compound obtained from isomerisation of the epoxide, and also isolated from liquid-phase oxidation of di*iso*butylene (Part I, p. 2162). Alcohol (XVI) is identical with that described by Byers and Hickinbottom (*J.*, 1948, 1328, 1331). However, they described (*loc. cit.*) as (VII) an alcohol, b. p. 170—174°, n_D^{20} 1·4292 (*p*-nitrobenzoate, m. p. 44—45°; 3 : 5-dinitrobenzoate, m. p. 74—75°), the properties of which are at variance with ours (b. p. 72—73·5°/12 mm., n_D^{20} 1·4441; *p*-nitrobenzoate, m. p. 30—35°; 3 : 5-dinitrobenzoate, m. p. 56°). Since the structure of our alcohol is established as (VII) by synthesis, Hickinbottom's compound must be something else, possibly a stereoisomer of (XVI). He (*loc. cit.*, p. 1333) gives m. p. 80° for the dinitrobenzoate of (XVI), but earlier (p. 1330) a dinitrobenzoate, m. p. 51°, was assigned the same probable structure, without comment on the anomaly. The second corresponds in m. p. with that of our (VII).

Products derived from Trimethylpentanal.—Hydrogenation of 2 : 4 : 4-trimethylpentanal (II), suitably in the vapour phase at 200° over a copper–kieselguhr catalyst, provided 2 : 4 : 4-trimethylpentan-1-ol (III). It was indeed possible to treat crude di*iso*butylene oxidation product, from which unchanged olefin had been removed, successively with an isomerisation catalyst and then hydrogen over the appropriate catalyst. The yield of trimethylpentanol so obtained was more than that theoretically possible from the epoxide content of the product, and presumably other compounds, such as the dimeric condensation products, suffered conversion into the aldehyde and thence into trimethylpentanol. Any olefin remaining in the oxidation product was unchanged by this procedure, and the dimethylpentanone was converted into 4 : 4-dimethylpentan-2-ol at less than one-third of the rate that the aldehyde was hydrogenated. Some esters of trimethylpentanol were prepared.

Oxidation of trimethylpentanal (II) with molecular oxygen, with metallic salts as catalysts, gave αγγ-trimethylvaleric acid (VIII).

A number of amines were prepared by reductive amination of trimethylpentanal (II), and one from 4 : 4-dimethylpentan-2-one (cf. Emerson, *Org. Reactions*, 1948, **4**, 174). High yields of 2 : 4 : 4-trimethylpentylamine (IX) were obtained by hydrogenating (II) in the presence of an excess of methanolic or aqueous ammonia. Raney nickel served as catalyst, and temperatures of 100—140° were necessary in an autoclave. The structure of (IX) was checked by preparing it by reducing the oily oxime of (II) with sodium and ethanol. The secondary amine, bis-2 : 4 : 4-trimethylpentylamine (X), was similarly prepared in excellent yield by reduction of the aldehyde (II) in presence of a twofold excess of the primary amine (IX). The excess of (IX) could be recovered; an excess of only 10% resulted in a much poorer yield. Reductive amination of 4 : 4-dimethylpentan-2-one under similar conditions gave a moderate yield (~50%) of 1 : 3 : 3-trimethylbutylamine.

The preparation of the tertiary amines, *NN*-dimethyl- and *NN*-diethyl-2 : 4 : 4-trimethylpentylamine (XI; R = Me and Et, respectively), by reduction of mixtures of (II) and dimethylamine or diethylamine, was less successful, yields of 27% and 29% respectively being obtained with small excess of amine. With 3 mols. of diethylamine to one of aldehyde, the yield was reduced to 15%.

Several attempts to make (IX) by reductive amination in the vapour phase were made, but only 20—22% yields of amines were obtained over copper or nickel on kieselguhr catalysts at 200—210° with contact times of 6—22 sec. The use of trimethylpentanal dissolved in 4 volumes of 5N-methanolic ammonia gave better results.

Bis-2 : 4 : 4-trimethylpentylamine (X) was methylated by the Eschweiler–Clarke modification of Leuckart's procedure, formaldehyde and formic acid being used. In

addition to the expected product, *N*-methyldi-(2 : 4 : 4-trimethylpentyl)amine (XVII) (66%), two further products, identified as *NN*-dimethyl-2 : 4 : 4-trimethylpentylamine (XI; R = Me) and 2 : 4 : 4-trimethylpentanal (II), were produced. From a number of small-scale experiments it was apparent that these two by-products occurred in approximately equimolar quantities. Corresponding by-products are reported to have occurred in the methylation of dibenzylamine (Clarke *et al.*, *J. Amer. Chem. Soc.*, 1933, **55**, 4571), and an analogous mechanism to that postulated may be applied in the present case.

The tertiary amines (XI; R = Me and Et) readily formed methobromides and methiodides. The amine (XVII) quaternised with more difficulty.

Experimental

Isomerisation of 1 : 2-*Epoxy*-2 : 4 : 4-*trimethylpentane to* 2 : 4 : 4-*Trimethylpentanal.—Liquid-phase.* (*a*) The best conditions for batch operation were as follows: Distilled epoxide (1 vol.) containing 90% of 1 : 2-epoxy-2 : 4 : 4-trimethylpentane, dissolved in *cyclo*hexane or benzene (3 vol.), was added to a stirred mixture of concentrated sulphuric acid (2 vol.) and water (2 vol.), kept below 30° by external cooling. The reaction was preferably conducted under an atmosphere of nitrogen or carbon dioxide. The isomerisation was very rapid, and the epoxide solution could be added as quickly as the removal of heat would allow. When the addition was complete, agitation was continued for a further 5 min. before separating the upper layer and shaking it with a small amount of potassium carbonate solution. The yield of aldehyde, by analysis of the resultant solution, was 89—92% on a 20-g. scale and 77—85% on a 400-g. scale. Equal yields of 2 : 4 : 4-trimethylpentan-1-ol could be obtained by direct hydrogenation of the solution of aldehyde. Distillation of the solution usually gave a somewhat lower yield of aldehyde; the fraction, b. p. 78°/100 mm., was obtained in the expected weight yield, but was only 90—92% pure by analysis by the hydroxylamine hydrochloride method.

(*b*) A 25% solution of epoxide in *cyclo*hexane and 50% aqueous sulphuric acid were fed countercurrent (epoxide at the lower end) into a 38 × 3·8 cm. (internal) glass column packed with porcelain saddles, and cooled externally by a water-jacket. Dispersion of the epoxide solution was effected by feeding in below the blades of a small stirrer operating in the lower part of the column. The two phases were allowed to separate at each end of the column; aldehyde–*cyclo*hexane solution continuously overflowed from the top of the column, and aqueous sulphuric acid was removed from the bottom. With a feed of 2·2 l. of epoxide solution per hr. per l. of reaction space (equivalent to a throughput of 456 g. of epoxide per hr. per l.) and an actual contact time of about 6 min., the yield of aldehyde was 71·4% on crude epoxide, or 82% on the 1 : 2-epoxide fed. No epoxide remained in the product, hence the rather low yields were due to occurrence of side-reactions. The average internal temperature of the column was kept at 20° during the experiment.

(*c*) Distilled epoxide (20·2 g.) containing 88% of the 1 : 2-isomer (by infra-red spectrum analysis), dissolved in an equal weight of *cyclo*hexane, was added slowly during 24 min. to 2N-sulphuric acid (200 ml.) with vigorous stirring under carbon dioxide. Steam was passed in so that the aldehyde steam-distilled out continuously as it was formed, along with the *cyclo*hexane. Analysis of the organic phase of the distillate indicated an aldehyde yield of 74% on epoxide taken, or 82% on the 1 : 2-isomer present.

Isomerisation in dilute sulphuric acid without steam-distillation gave variable yields, owing not only to the greater chance of the aldehyde decomposing, but also to greater formation of trimethylpentanediol.

(*d*) Epoxide stirred with 90% phosphoric acid as described in (*a*) above gave a 92% yield of aldehyde when the volume ratio of acid to epoxide solution was 1 : 100, and 88% when the volumes were equal.

(*e*) Aqueous hydrochloric or toluene-*p*-sulphonic acid gave inferior results.

(*f*) Some solid catalysts, mainly of the Friedel–Crafts type, were examined. In general, 1 : 2-epoxide solutions were dripped slowly on to a fixed amount (2%) of catalyst, then stirred under nitrogen at room temperature for 15 min. and finally heated to 70° for 30 min. The yield of aldehyde was determined by hydroxylamine titration after preliminary neutralisation. Details of the runs are given in Table 1.

The following gave no isomerisation (in *cyclo*hexane): Nickel chloride, mercuric chloride, alumina.

Vapour-phase. The apparatus consisted of a Pyrex U-tube immersed in a fusible-metal bath. One arm, 15 mm. in diameter, was filled with granules of alumina (Peter Spence, 10—18

mesh; previously used; sulphur-free) supported on a sintered-glass plate (catalyst volume 12—18 ml.). Epoxide was introduced into the other arm, which acted as a vaporiser and pre-heater. The epoxide content of the feed was determined by infra-red spectrum analysis, and the degree of isomerisation was measured by titration of aldehyde and epoxide in the product.

TABLE 1.

Catalyst	Solvent	Concn. of epoxide, %	Yield of aldehyde, %	Catalyst	Solvent	Concn. of epoxide, %	Yield of aldehyde, %
$ZnCl_2$ ...	None	—	41	$SnBr_4$ [5]	*cyclo*Hexane	25	78 [1, 3]
,, ...	*cyclo*Hexane	25	73 [1]	$SnCl_2$ [6]	Di*iso*butylene	25	75 [7]
,, ...	,,	12·5	84	BF_3,Et_2O	,,	25	62 [7]
,, ...	Benzene	25	84 [1]	$TiCl_4$	*cyclo*Hexane	25	66 [7]
,, ...	Di*iso*butylene	25	88 [2]	NaH_2PO_4	,,	25	6
$FeCl_3$ ...	None	—	25	$Al_2(SO_4)_3$	,,	25	8
,, ...	*cyclo*Hexane	25	91 [3]	Potash alum ...	,,	25	4 [7]
,, ...	,,	12·5	87·5	Zeocarb H.I. ...	,,	25	8
,, ...	Benzene	25	87·5 [4]	,, ...	Benzene	25	22
,, ...	Di*iso*butylene	25	48 [2]	Supercel	*cyclo*Hexane	25	4 [1]
$MgCl_2$ ...	*cyclo*Hexane	25	5·5	Fuller's earth [8]	,,	25	58
$CoCl_3$ ...	,,	25	5				

[1] Reaction is substantially complete after 15 min. at room temp. [2] Reaction is substantially complete after 15 min. at room temp., then 15 min. at 70°. [3] Final heating at 80° (30 min.). [4] Final heating for 15 min. at 70°; only 62% yield after 30 min. [5] 5% on epoxide. [6] 1% on epoxide. [7] Not heated. [8] Fulmont 700.

This procedure was adequate for a comparison of results under different conditions. The epoxide analysis (by hydrogen chloride–ether) would give a low result (cf. Part I, p. 2163), and applied to a first approximation only to the 1 : 2-isomer. The carbonyl analysis would also include dimethylpentanone which was originally present in known quantity in the epoxide fed and so could be allowed for in the result. The 2 : 3-epoxide gives only small amounts of keto-compounds which react with hydroxylamine in the cold (see below). In all runs except those in which obvious decomposition occurred, the weight balance was quantitative.

Highest aldehyde yields were obtained between 280° and 340°, and varied between 83 and 87% by weight, or 95—99·5% on the 1 : 2-epoxide used. The yield was unchanged over a variation in contact time (calculated as the vapour flow at the reaction temperature through an empty reaction vessel) between 2 sec. and about 100 sec. The catalyst had a life of >100 hr., although it became covered with a thin film of carbon. The average aldehyde yield, from an epoxide fraction of 92·7% purity, was 95% on the 1 : 2-epoxide fed; the total epoxide isomerised was 1075 g. per g. of catalyst.

Larger-scale experiments were carried out in an electrically-heated inclined Pyrex tube, 75 × 2·5 cm. (internal). The heat removal was not so efficient, and a hot zone formed in the catalyst at the feed end. Nevertheless, provided that contact time was sufficiently long (above 4 sec.) to prevent gross overheating, results as favourable as in the smaller apparatus were attained.

Granulated acid-washed fuller's earth (8—10 mesh) gave, after an initial period of rather lower yields, 98% of aldehyde on 1 : 2-epoxide fed. It appeared to be less vigorous and easier to control than alumina, but its catalytic life was not determined. Pumice or kieselguhr impregnated with phosphoric acid gave up to 90% yields under suitable controlled conditions; it was necessary to dilute the entering epoxide vapour, and to avoid the combination of high acid content and high feed rate, which resulted in charring. Oxidised aluminium (Dural) turnings gave a 76% yield.

Of vapour-phase catalysts, sulphur trioxide gave a 74% yield with considerable charring; dibutyl hydrogen phosphate 10—12%; and sulphur dioxide, although it entered into reaction with the epoxide at room temperature with evolution of heat, gave only 3—4% of aldehyde at 250°.

Reaction with acetic anhydride and sulphuric acid. Epoxide (128 g.) was added dropwise to stirred acetic anhydride (200 g.) containing sulphuric acid (2 g.). The reaction was highly exothermic, and the temperature was controlled below 60° by the rate of addition. After an hour, the sulphuric acid was neutralised with an excess of powdered anhydrous sodium acetate, and after filtration most of the acetic anhydride was removed under reduced pressure. The

residue was partitioned between ether and water, and the alkali-washed ethereal layer distilled to give two main fractions, (i) b. p. 76°/12 mm., n_D^{20} 1·4338 (22·1 g.), and (ii) b. p.114°/12 mm., n_D^{20} 1·4296 (82·9 g.). Fraction (i) had a hydrolysis equivalent of 177 (calc., 170), and was shown spectroscopically to be impure 2-*neo*pentylallyl acetate (see below). This was confirmed by hydrolysis to the alcohol, b. p. 75—80°/20 mm., n_D^{20} 1·4440 (3 : 5-dinitrobenzoate, m. p. 47—48° undepressed by authentic material).

Fraction (ii) gave hydrolysis equivalent 122 (calc. for the glycol diacetate, 115), but was not identical with 2 : 4 : 4-trimethylpentane-1 : 2-diol diacetate (Part III, p. 2190). When warmed with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, it gave a precipitate of 2 : 4 : 4-trimethylpentanal 2 : 4-dinitrophenylhydrazone, but the glycol diacetate does likewise. It was rather resistant to alkaline hydrolysis; 40 g. of fraction (ii) were refluxed for 6 hr. with 20 g. of sodium hydroxide in 200 ml. of water and 50 ml. of ethanol, and the product was extracted and separated roughly into two fractions, boiling above and below 50°/12 mm., by rapid distillation without a column. The first fraction (10·1 g.) on refractionation through a column gave almost exclusively 2 : 4 : 4-trimethylpentanal, b. p. 42°/12 mm., n_D^{20} 1·4138 (dinitrophenylhydrazone, m. p. 145°). The second fraction yielded a little 2 : 4 : 4-trimethylpentane-1 : 2-diol, b. p. 104—105°/10 mm. (3·0 g.; solidified on cooling). The presence of 15% of diol in the hydrolysis product was also inferred from periodate titration.

Fraction (ii) was therefore presumed to consist of 15% of 2 : 4 : 4-trimethylpentane-1 : 2-diol diacetate (V) and the remainder of 2 : 4 : 4-*trimethylpentylidene diacetate* (IV). The latter was synthesised as follows: 2 : 4 : 4-trimethylpentanal (50 g.) was added slowly to acetic anhydride (100 ml.) containing sulphuric acid (2 g.), and, by the procedure of the last experiment, 37·8 g. of the diacetate were obtained, b. p. 112—114°/10 mm., n_D^{20} 1·4274 (Found: C, 63·4; H, 9·8%; equiv., 119. $C_{12}H_{22}O_4$ requires C, 62·5; H, 10·1%; equiv., 115). Infra-red spectroscopy showed that this was identical with the main component of fraction (ii) above. It did not give better analytical figures after repeated redistillations.

Isomerisation of 1 : 2-*Epoxy*-2 : 4 : 4-*trimethylpentane to* 2-neo*Pentylprop*-2-*en*-1-*ol.*—*In alcohol.* (*a*) The epoxide (100 g.) was heated in ethanol (500 ml.) to 220° in an autoclave for 5 hr. Distillation under reduced pressure removed alcohol and much unchanged epoxide, and the remainder was fractionated through a column. A main fraction (15·7 g.), b. p. 71—74°/12 mm., n_D^{20} 1·4409, was obtained, which had the properties of an unsaturated primary alcohol. It yielded a *p*-nitrobenzoate, m. p. 30—35° (crystallised from alcohol between 20° and −50°), and a 3 : 5-dinitrobenzoate, m. p. 52—53°. The carbon skeleton was proved by hydrogenation, over Adams's catalyst at room temperature and pressure, to 2 : 4 : 4-trimethylpentan-1-ol (3 : 5-dinitrobenzoate, m. p. 74° not depressed by authentic material). The unsaturated alcohol formed an acetate, b. p. 73°/15 mm., n_D^{20} 1·4280 (Found: equiv., 170. Calc. for $C_{10}H_{18}O_2$: equiv., 170). It was identified by comparison with synthetic material (see below) as 2-*neo*pentylprop-2-en-1-ol.

(*b*) A similar experiment but with methanol in place of ethanol gave the same product, with additional indications of some methoxytrimethylpentanol; the latter could not, however, be definitely identified.

Without solvent. In the following experiments, 10 g. of the epoxide were heated in a Carius tube and then distilled, the following fractions being collected: (i) b. p. 40—50°/10 mm. (unchanged epoxide, aldehyde), (ii) 50—72°/10 mm. (intermediate), (iii) 72—85°/10 mm. (trimethylpentenol and -pentanol), (iv) above 85°/10 mm., (v) undistillable residue. The product (iii) was identified by conversion into the 3 : 5-dinitrobenzoate, which was either that of 2-*neo*pentylprop-2-en-1-ol or of 2 : 4 : 4-trimethylpentan-1-ol. No attempt was made to fractionate the esters, so that it is possible that the more readily formed and crystallised trimethypentanol derivative may mask the presence of the trimethylpentenol. Attempts to estimate the percentage of unsaturated alcohol by bromide–bromate titration gave high and inconsistent values, sometimes well over 100% of apparent trimethylpentenol. Results are collected in Table 2.

Isomerisation in liquid paraffin. Epoxide (10 g.) was heated in medicinal paraffin (20 ml.) for 18 hr. at 275°, and in the same way gave (i) 1·2, (ii) 1·2, (iii) 1·5 g. Fraction (iii) showed only 10% of trimethylpentenol by titration, and gave the dinitrobenzoate of the trimethylpentanol.

2 : 4 : 4-*Trimethylpent*-2-*en*-1-*ol.*—β-*tert.*-Butyl-α-methylacraldehyde (αγγ-trimethylcrotonaldehyde) (23·5 g.; Hall, Hadley, Heap, and Jacobs, *loc. cit.*) was heated with 3N-aluminium *iso*propoxide in *iso*propanol (63 ml.) at the base of a fractionating column. Acetone was withdrawn from the head of the column until nearly the calculated amount had collected. The residue in the base was acidified and worked up to yield 2 : 4 : 4-trimethylpent-2-en-1-ol, b. p. 75—77°/20 mm. (13·0 g., 55%), n_D^{20} 1·4501. The 3 : 5-dinitrobenzoate formed flat needles,

m. p. 80° (Hickinbottom, *J.*, 1948, 1333, gives b. p. 177·5—178·5°/760 mm., n_D^{20} 1·4459; dinitrobenzoate, m. p. 80°).

2-neo*Pentylprop*-2-*en*-1-*ol*.—α-*neo*Pentylacraldehyde (22·3 g.) was similarly reduced with *iso*propoxide solution (60 ml.), yielding of 2-neo*pentylprop*-2-*en*-1-*ol* (7·0 g., 31%), b. p. 72—73·5°/12 mm., n_D^{20} 1·4441 (Found: C, 74·7; H, 12·2. $C_8H_{16}O$ requires C, 75·0; H, 12·6%). This was identical in infra-red spectrum with the unsaturated alcohol obtained by heating the 1 : 2-epoxide. It formed a 3 : 5-*dinitrobenzoate*, m. p. 56° not depressed by the derivative obtained by heating the epoxide (Found: C, 55·8; H, 5·6. $C_{15}H_{18}O_6N_2$ requires C, 55·8; H, 5·7%), and a 1-*naphthylurethane*, m. p. 83—85° (from light petroleum) (Found: C, 76·7; H, 7·8. $C_{19}H_{23}O_2N$ requires C, 76·8; H, 7·8%).

TABLE 2.

Conditions:		Wt. of products, g.					Identification of (iii) by dinitrobenzoate
Time, hr.	Temp.	(i)	(ii)	(iii)	(iv)	(v)	
24	200°	5·4	1·0	1·3	0	1·2	Trimethylpentenol
1·75	250	6·7	0	2·2	0	0	Unidentified
4	250	2·1	1·1	3·0	1·1	1·5	Trimethylpentenol
7	250	1·8	1·6	2·9	0·9	1·3	Trimethylpentanol (?)
18	250	0	0·6	3·1	2·6	1·7	Trimethylpentanol
2	275	3·1	2·3	3·6	0	0·8	Mixture

Isomerisation of 2 : 3-*Epoxy*-2 : 4 : 4-*trimethylpentane*.—(*a*) (cf. Hickinbottom, *J.*, 1948, 1333). The 2 : 3-epoxide, shaken for 1 hr. with 10% (wt.) aqueous sulphuric acid, gave mainly 2 : 4 : 4-trimethylpent-1-en-3-ol (XIII), identified as its 3 : 5-dinitrobenzoate, m. p. 120—121° (Hickinbottom, *loc. cit.*, gives 123°), and a little 2 : 4 : 4-trimethylpentane-2 : 3-diol, m. p. 62—63° (Byers and Hickinbottom, *ibid.*, p. 286, give m. p. 65—66°). The mixed product yielded a small amount of the orange-red 2 : 4-dinitrophenylhydrazone of 2 : 2 : 4-trimethylpentan-3-one (XV), m. p. and mixed m. p. 154—156°.

(*b*) In the vapour phase over alumina at 279—290°, the 2 : 3-epoxide (34 g.) gave a liquid product (26 g.), which was distilled to give the following fractions: (i) b. p. 123·5—127° (4 g.; 7·3% of C_8 ketone by titration), (ii) 127—135° (18 g.; 25% of ketone), (iii) 135° (8 g.; 29% of ketone), (iv) 110°/130 mm. (4 g.; 61% of ketone). In spite of the low carbonyl values, no other functional groups were detectable by infra-red analysis of the fractions, whereas the C=O bands were strong. It appeared that a carbonyl compound that did not react readily with hydroxylamine had been produced. Fractions (iii) and (iv) both yielded the orange-red dinitrophenylhydrazone, m. p. and mixed m. p. 158—160°, of 2 : 2 : 4-trimethylpentan-3-one. Fractions (i) and (ii) yielded dinitrophenylhydrazones which melted over a range; from (ii) was eventually obtained a derivative, m. p. 97—100°, depressed by admixture with the hydrazone of 4 : 4-dimethylpentan-2-one.

(*c*) From similar isomerisation (on a larger scale) of the dimethylpentanone–2 : 3-epoxide azeotrope were obtained the same products, and also a small quantity of a volatile solid, m. p. 109—119°, b. p. 46—52°/12 mm., with a strong odour of camphor. It gave a yellow 2 : 4-dinitrophenylhydrazone, m. p. 157—159°. When kept in contact with air for 2—3 months the original substance changed into an odourless acidic solid, m. p. 195—197° (sealed tube) after one recrystallisation from ethyl acetate. This was probably ααββ-tetramethylbutyric acid (cf. Byers and Hickinbottom, *ibid.*, p. 1336), and so the camphoraceous solid was 2 : 2 : 3 : 3-tetramethylbutanal (XIV), which is recorded as having a yellow dinitrophenylhydrazone, m. p. 163—164° (*idem*, *ibid.*, p. 286).

A sample of 2 : 2 : 4-trimethylpentan-3-one was synthesised by Favorsky and Fritzmann's method (*J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1351); this gave the 2 : 4-dinitrophenylhydrazone as orange-red leaflets, m. p. 161—162° (Byers and Hickinbottom, *J.*, 1948, 287, record m. p. 163—164°).

Hydrogenation of 2 : 4 : 4-*Trimethylpentanal to Trimethylpentanol*.—The apparatus used was an electrically-heated Pyrex tube, 2·5 cm. in internal diameter, packed with 290 g. of copper–kieselguhr catalyst in the form of pellets (3 mm. diameter × 1 mm. thick). The liquid feed was first passed through a heated copper coil where it was vaporised and mixed with the hydrogen. The optimum conditions were: reaction temperature, 200° ± 10°; 6—7 moles of hydrogen per mole of aldehyde fed; and a contact time of *ca.* 20 sec. The product was separated by fractional distillation.

It was advantageous to carry through the preparation by removing unchanged di*iso*butylene

from the oxidation product as far as possible by distillation, passing the residue through the isomerisation process under the conditions indicated above, and then hydrogenating the product by the procedure just described. Thus, crude isomerised oxidation product (518 g.) gave 508 g. of liquid product, which by distillation followed by chemical and infra-red analysis was shown to consist of di*iso*butylene (4·8%), dimethylpentanone (5·7%), trimethylpentanone (8·7%), trimethylpentanal (1·5%), 4 : 4-dimethylpentan-2-ol (4·6%), 2 : 4 : 4-trimethylpentan-3-ol (4·5%), 2 : 4 : 4-trimethylpentan-1-ol (59·9%), and unknown material (10·1%, mainly in the distillation residue). The main fraction of 2 : 4 : 4-trimethylpentan-1-ol (267·2 g.), b. p. 168—169°/740 mm., was substantially pure.

The vapour pressure of 2 : 4 : 4-trimethylpentan-1-ol was as follows :

Pressure, mm.	20	40	60	100	200	400	760
Temp.	79·7°	93·1°	101·6°	113·6°	131·2°	151·2°	172·4°

Esters of 2 : 4 : 4-*Trimethylpentan*-1-*ol.*—A number of esters were prepared as in the following example : Adipic acid (36·5 g.; 0·25 mole), trimethylpentanol (100 g.; 0·77 mole), benzene (19 g.), and concentrated sulphuric acid (0·1 ml.) were heated under reflux, the water being removed by means of a Dean and Stark head. When the reaction was completed (6 hr.) the benzene was removed, and the crude ester washed and distilled. Other esters were prepared in a similar manner, except the phosphate which was made by slowly adding trimethylpentanol (109 g.) to a stirred solution of phosphorus oxychloride (38 g.) in benzene (107 g.); when the addition was complete the mixture was warmed on the steam-bath until evolution of hydrogen chloride ceased. The ester was then washed and distilled. The following esters were thus prepared :

	B. p./mm.	n_D^{20}	Equiv. Reqd.	Equiv. Found
Adipate	178°/1	1·4452	185	186
αγγ-Trimethylvalerate	92—93°/1	1·4307	256	259
Fumarate	168—172°/2	1·4540	170	168
Maleate	167°/3	1·4518	170	171
Pimelate	192°/1·5	1·4461	192	189
Orthophosphate	184°/2	1·4395	—	—
Oleate	208°/1	1·4547	394	378
cyclo*Hexene*-3-*carboxylate*	112°/2	1·4600	239	240

Oxidation of 2 : 4 : 4-*Trimethylpentanal to αγγ-Trimethylvaleric Acid.*—Oxygen was passed through trimethylpentanal (410 g.) containing manganese naphthenate (" Novenate," A. Boake Roberts & Co.; 1 g.) with rapid stirring, until absorption became very slow. Water separated during oxidation. The product was fractionally distilled, and trimethylvaleric acid came over at 90—94°/2 mm.; a higher fraction, b. p. 110—120°/1 mm., may have been the anhydride. Some material boiling below the aldehyde was always obtained, but could not be separated or identified. The results obtained at different oxidation temperatures may be summarised :

Temp.	Time, hr.	O_2 absorbed (% of theory)	Peroxide, mole/l. Max.	Peroxide, mole/l. Final	Yield of acid (% on aldehyde charged)
50°	8	33	0·48	—	42
10—20	12·5	73	0·33	0·13	60
0	4·5	76	—	0·05	73·5

The oxidation rate decreased and degradation increased with increase of temperature. It appeared from further results that at low temperatures (0—10°) an unstable peroxide was formed (probably aldehyde peroxide), which decomposed (particularly on heating) to give mainly acid, whilst at higher temperatures (30—50°), a more stable peroxide was formed which was not greatly decomposed under the conditions of reaction.

A vanadium naphthenate catalyst gave more irregular results and one explosion. At low temperatures oxygen was taken up rapidly, but the catalyst was apparently incapable of decomposing the peroxide formed.

In order to convert it into the chloride, 100 g. of trimethylvaleric acid were warmed with 70 ml. of thionyl chloride until gas evolution had ceased and the mixture was boiling. The product was fractionated through a short column, and the acid chloride collected at 164—165°/750 mm. The yield was 107 g. (95% of theory).

Amines derived from 2 : 4 : 4-*Trimethylpentanal and* 4 : 4-*Dimethylpentan*-2-*one.*—2 : 4 : 4-

Trimethylpentylamine (IX). (*a*) 2 : 4 : 4-Trimethylpentanal (200 g., 1·56 moles) and 10N-methanolic ammonia (500 ml., 5 moles) were hydrogenated at 30 atm. and 120° in the presence of Raney nickel. Reduction was complete after 2 hr. The methanol was evaporated from the filtered solution, and then benzene was added and water removed as the azeotrope. Finally 2 : 4 : 4-trimethylpentylamine, b. p. 79—84°/78 mm. (173·2 g., 84%), was distilled out. The picrate gave no depression of m. p. in admixture with that prepared as in (*c*) below.

(*b*) Trimethylpentanal dissolved in four times its volume of 4N-methanolic ammonia was passed, with a tenfold excess of hydrogen, over pelleted nickel on kieselguhr (28% Ni) at 200°. The contact time was 20 sec. Conversions of 45% into 2 : 4 : 4-trimethylpentylamine and 16% into bis-2 : 4 : 4-trimethylpentylamine were thus attained.

(*c*) Trimethylpentanal (10 g.), hydroxylamine hydrochloride (10 g.), potassium acetate (15 g.), methanol (100 ml.), and water (50 ml.) were refluxed together for 1 hr. The mixture was poured into water, the oily layer extracted with ether, the extract washed successively with water, 2N-hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated to yield the oily oxime. This was dissolved in dry ethanol (500 ml.) and added in one portion to sodium (50 g.) cut in small pieces in a 2-l. flask fitted with an efficient reflux condenser. The reaction was allowed to proceed vigorously with only occasional cooling to prevent flooding of the condenser. The mixture was finally heated on the steam-bath until all the sodium had reacted, poured into a large quantity of water, and the basic fraction isolated in ether. From it, 2 : 4 : 4-*trimethylpentylamine* (22%) was obtained, b. p. 45—47°/12 mm., 150—152°/735 mm., n_D^{20} 1·4280 (Found: C, 73·5; H, 14·5; N, 10·9%; equiv., 130. $C_8H_{19}N$ requires C, 74·3; H, 14·8; N, 10·8%; equiv., 129). The carbon values for this compound were persistently low. The *picrate* crystallised from aqueous ethanol in yellow plates, m. p. 190° (Found: C, 47·2; H, 5·9; N, 15·6. $C_8H_{19}N,C_6H_3O_7N_3$ requires C, 46·9; H, 6·2; N, 15·6%). The *sulphate* crystallised in colourless plates, m. p. 268—272°, from hot water on dilution with ethanol (Found: N, 7·6. $2C_8H_{19}N,H_2SO_4$ requires N, 7·9%).

Bis-2 : 4 : 4-*trimethylpentylamine* (X).—2 : 4 : 4-Trimethylpentylamine (197 g.; 88% pure; 1·34 mole), 2 : 4 : 4-trimethylpentanal (105 g.; 85% pure; 0·70 mole), methanol (150 ml.), and Raney nickel were hydrogenated at 50 atm. and 110—125°. Reaction was complete after 6 hr. Distillation of the filtered product afforded the secondary *amine*, b. p. 121—124°/11 mm., n_D^{20} 1·440 (154 g., 92% based on aldehyde) (Found: C, 79·0; H, 14·3; N, 5·8. $C_{16}H_{35}N$ requires C, 79·6; H, 14·5; N, 5·8%). The *hydrochloride* had m. p. 134—137° after recrystallisation from ethyl acetate (Found: N, 4·8. $C_{16}H_{35}N,HCl$ requires N, 5·0%).

N-*Methylbis*-2 : 4 : 4-*trimethylpentylamine*.—98% Formic acid (50 ml.) was added carefully to bis-2 : 4 : 4-trimethylpentylamine (50 g.), so that the temperature of the mixture remained below 40°. 40% Aqueous formaldehyde (50 ml.) was then added, and the mixture warmed until evolution of carbon dioxide began. When this was substantially complete, the mixture was refluxed for 2 hr., then poured into a large volume of water and basified with sodium hydroxide. The oil which separated was isolated, by use of ether, and distilled. The main fraction, b. p. 120—130°/12 mm. (b. p. 127—128°/13 mm., n_D^{20} 1·4377, after redistillation) was the tertiary *amine* (XVII) (34·8 g., 66%) (Found: C, 80·3; H, 14·7; N, 5·2%; equiv., 258. $C_{17}H_{37}N$ requires C, 79·9; H, 14·6; N, 5·5%; equiv., 255). The *picrate* crystallised from ethanol in yellow plates, m. p. 128—129° (Found: C, 57·2; H, 8·2; N, 11·7. $C_{17}H_{37}N,C_6H_3O_7N_3$ requires C, 57·0; H, 8·3; N, 11·6%), and the *hydrobromide* had m. p. 238° (from aqueous ethanol) (Found: C, 60·2; H, 11·1; N, 4·1. $C_{17}H_{37}N,HBr$ requires C, 60·7; H, 11·4; N, 4·2%).

The fore-runnings of the distillation (b. p. 30—120°/12 mm.) were separated into basic and neutral material. Distillation of the former gave *NN*-dimethyl-2 : 4 : 4-trimethylpentylamine, b. p. 47—50°/10 mm., n_D^{20} 1·4220, equiv., 158, m. p. and mixed m. p. of picrate, 107° (cf. below). The neutral fraction boiled mainly at 143—148°, n_D^{20} 1·4178, and contained aldehyde equivalent to 80% of 2 : 4 : 4-trimethylpentanal. The 2 : 4-dinitrophenylhydrazone, m. p. 136—137°, gave no depression of m. p. when mixed with the derivative of authentic 2 : 4 : 4-trimethylpentanal.

Quaternisation of methylbis-2 : 4 : 4-trimethylpentylamine (2 g.) with methyl iodide (5 g.) at 110° for 2 hr. in a Carius tube gave the *methiodide* (1·35 g.), which had m. p. 198° (decomp.) after recrystallisation from aqueous ethanol (Found: N, 3·0. $C_{18}H_{40}NI$ requires N, 2·8%).

Quaternisation of the amine (XVII) (20 g., 0·0785 mole) with methyl bromide (16 g., 0·168 mole) in ethyl acetate (50 ml.) containing sodium iodide (1 crystal) at 110° for 4 hr. in Carius tubes afforded a crude solid (23·0 g.) insoluble in the solvent. The mother-liquor contained unchanged amine (18%). The solid was taken up in chloroform and washed with 2N-sodium hydroxide to decompose the amine hydrobromide which it contained. The chloroform layer

was reconcentrated, and the residual sticky solid triturated with ethyl acetate. On recrystallisation from ethanol–ethyl acetate the m. p. of the *methobromide* (18·9 g.) was raised to 209—210° (Found: C, 62·0; H, 11·4. $C_{18}H_{40}NBr$ requires C, 61·7; H, 11·5%); a mixed m. p. with hydrobromide described above was 186—189°.

1 : 3 : 3-*Trimethylbutylamine*.—4 : 4-Dimethylpentan-2-one (68 g., 0·60 mole) and 10N-methanolic ammonia (150 ml., 1·5 moles) were hydrogenated at 55 atm. and 120—140° over Raney nickel. **1 : 3 : 3-Trimethylbutylamine**, b. p. 118—121°, n_D^{20} 1·416, was fractionated out of the product (49%). The *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 181—182° (Found: C, 45·6; H, 6·0; N, 16·5. $C_7H_{17}N,C_6H_3O_7N_3$ requires C, 45·3; H, 5·9; N, 16·3%).

NN-*Diethyl*-2 : 4 : 4-*trimethylpentylamine* (XI; R = Et).—A mixture of trimethylpentanal (400 g., 3·1 moles), diethylamine (235 g., 3·2 moles), methanol (200 ml.), and Raney nickel was reduced at 100° and 50 atm. pressure of hydrogen in the usual way. The main fraction had b. p. 71—76°/14 mm. (93·5 g., 16%) and redistillation afforded **NN-*diethyl*-2 : 4 : 4-*trimethylpentylamine***, b. p. 70—71°/10 mm., n_D^{20} 1·4272, K_b 10^{-4} (Found: C, 77·7; H, 14·6; N, 7·9%; equiv., 182. $C_{12}H_{27}N$ requires C, 77·8; H, 14·7; N, 7·6%; equiv., 185). The *picrate*, after recrystallisation from aqueous ethanol, had m. p. 96—97° (Found: N, 13·4. $C_{12}H_{27}N,C_6H_3O_7N_3$ requires N, 13·5%). From the high-boiling residue of the distillation, some *NN*-diethyl-2-hydroxy-2 : 4 : 4-trimethylpentylamine, b. p. 90—100°/10 mm. (7·0 g.), was obtained, and identified with the material otherwise prepared (Part III) by a mixed m. p. of the picrate, m. p. 104—105°.

The amine was quaternised by refluxing it with excess of methyl iodide on a steam-bath for 1 hr. The *methiodide* obtained had m. p. 101—102° after recrystallising from acetone–ether and drying at 0·2 mm. for 3 hr. (Found: C, 47·6; H, 9·2; I, 39·3. $C_{13}H_{30}NI$ requires C, 47·7; H, 9·2; I, 38·8%). The *methobromide*, prepared from the amine and methyl bromide in benzene at 110° for 5 hr., had m. p. 110° after recrystallisation from acetone–ethyl acetate, and was very hygroscopic (Found: Br, 28·8. $C_{13}H_{30}NBr$ requires Br, 28·6%).

NN-*Dimethyl*-2 : 4 : 4-*trimethylpentylamine* (XI; R = Me).—A mixture of 2 : 4 : 4-trimethylpentanal (240 g., 1·87 moles), 33% aqueous dimethylamine (350 ml., 1·33 moles), ethanol (400 ml.), and Raney nickel was reduced as in the experiment described above, giving *NN*-dimethyl-2 : 4 : 4-trimethylpentylamine, b. p. 53—63°/11 mm., n_D^{20} 1·423 (79 g., 27%; 96% pure by base titration). The *picrate* had m. p. 105—196° after recrystallisation from ethanol (Found: C, 49·4; H, 6·2; N, 14·5. $C_{10}H_{23}N,C_6H_3O_7N_3$ requires C, 49·7; H, 6·7; N, 14·5%). The *hydrochloride* had m. p. 167—168° after recrystallisation from *iso*propanol–ether (Found: N, 6·9. $C_{10}H_{23}N,HCl$ requires N, 7·2%).

The amine was quaternised by leaving it with an excess of methyl iodide in ethyl acetate for 2 days. The *methiodide* which separated as a white solid (7·7 g., 73%) had m. p. 238° (decomp.) after recrystallisation from acetone–ethyl acetate (Found: C, 44·2; H, 8·5. $C_{11}H_{26}NI$ requires C, 44·1; H, 8·8%).

The amine (30 g.), methyl bromide (20 g.), and ethyl acetate (100 ml.) were heated in a silver-lined autoclave to 140—150° for 4 hr. The crystalline, hygroscopic *methobromide* was filtered off and recrystallised from ethanol–ethyl acetate; the yield was 35·1 g. (73%) (Found: Br, 31·9. $C_{11}H_{26}NBr$ require Br, 31·7%). By further recrystallisation a m. p. of 275° (decomp.) was attained.

We are indebted to Mr. H. C. Highet for the vapour-pressure data, and to Mr. A. R. Philpotts for carrying out the spectroscopic analyses. We also thank the Directors of the Distillers Company Ltd. for permission to publish this paper.

THE DISTILLERS COMPANY LTD., RESEARCH AND DEVELOPMENT DEPARTMENT,
GREAT BURGH, EPSOM, SURREY. [*Received, December 29th,* 1953.]

Oxidation Products of Diisobutylene. Part III. Products from Ring-opening of 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane.*

By A. R. Graham, A. F. Millidge, and D. P. Young.

[Reprint Order No. 4940.]

The interaction of 1 : 2-epoxy-2 : 4 : 4-trimethylpentane with water, alcohols, amines, acids, and various other reagents has been examined. Ring-opening reactions in presence of acidic catalysts take place under mild conditions, but are accompanied by rearrangement to 2 : 4 : 4-trimethylpentanal and other side-reactions. On the other hand, interaction of the epoxide with basic reagents or under alkaline conditions usually gives good yields of the expected product, but high temperatures are necessary in order to attain reasonable rates of reaction.

The structures of the majority of the adducts have been proved by synthesis or otherwise, and accord with the general rule that with a reagent HX, the epoxide under acid conditions gives $CH_2Bu^t{\cdot}CMeX{\cdot}CH_2{\cdot}OH$, and under basic conditions (and also with hydrogen chloride in dry ether) gives $CH_2Bu^t{\cdot}CMe(OH){\cdot}CH_2X$. From reaction with various alcohols, a series of isomeric derivatives has thus been prepared by varying the catalyst.

The epoxide is hydrated to 2 : 4 : 4-trimethylpentane-1 : 2-diol in either dilute acid or alkali. Alkaline hydration has been successfully applied to some other epoxides that are sensitive to acids. The 1 : 2-diol is easily converted by acids into 2 : 4 : 4-trimethylpentanal or its cyclic acetal with the diol.

This paper describes the products obtained from 1 : 2-epoxy-2 : 4 : 4-trimethylpentane by reactions involving ring-opening without pinacolic rearrangement. We find that 1 : 2-epoxy-2 : 4 : 4-trimethylpentane (I) undergoes the conventional reactions of epoxides, but that the great ease of rearrangement to trimethylpentanal is a complicating factor. This has already been noted by Hickinbottom (*J.*, 1948, 1332). Ring-opening with acidic reagents or acid catalysts is rapid and exothermic, but is always accompanied by formation of 2 : 4 : 4-trimethylpentanal or its " dimer," and sometimes 2-*neo*pentylprop-2-en-1-ol as well. With basic reagents and alkaline catalysts, on the other hand, the epoxide reacts very sluggishly, and temperatures of 150° or higher are frequently necessary for reaction at a reasonable rate. An exception is the case of thiols, which react exothermally at room temperature in presence of alkalis. A summary of the reactions carried out is given in Table 1.

Hydration.—Hickinbottom (*loc. cit.*) expressed surprise at the preponderance of side-reactions during attempted hydration of the epoxide with aqueous sulphuric acid, although he quoted some other epoxides which behaved similarly. Prileschajev (*J. Russ. Phys. Chem. Soc.*, 1910, **42**, 1404) hydrated mixed 1 : 2- and 2 : 3-epoxy-2 : 4 : 4-trimethylpentane with water at room temperature, but found that the reaction was very slow. Danilow and Venus-Danilowa (*Ber.*, 1927, **60**, 1061) reduced isomerisation of 1 : 2-epoxy-2-phenylpropane by hydrating it with very dilute acid, in this case hydrochloric. Application of this technique was successful with 1 : 2- and 2 : 3-epoxytrimethylpentane; by agitation with 0·1N-sulphuric or -nitric acid at room temperature, a gently exothermic reaction ensued, and the diols were obtained after some hours in about 70% yields. This concentration of acid was the optimum; 0·1N-hydrochloric acid, however, gave very poor yields. All attempts to accelerate the reaction by warming only led to an increase of isomerisation; even when refluxed with water, the product was mainly aldehyde. Boiling aqueous alcohol gave some diol, but in this case the mixture was probably sufficiently acid (pH 3) to catalyse hydration.

The occurrence of some rearrangement, even under optimum conditions, during acid hydration suggested the possibility of hydration by aqueous alkali. Alkaline hydration of epoxides has in the past been neglected in favour of acidic catalysis, which is normally much more effective. Indeed, the existence of alkaline catalysis at all was demonstrated

* Part II, preceding paper.

only recently (Lichtenstein and Twigg, *Trans. Faraday Soc.*, 1948, **44**, 905), although alkaline hydration had been employed in a few cases previously (Porret, *Helv. Chim. Acta*, 1944, **27**, 1321; Levene and Walti, *J. Biol. Chem.*, 1927, **73**, 263; Leroux, *Ann. Chim.*, 1910, **21**, 500; Bamberger and Lodter, *Annalen*, 1895, **288**, 100).

1 : 2-Epoxy-2 : 4 : 4-trimethylpentane was very stable to aqueous alkali of any strength at the atmospheric boiling point, and could in fact be steam-distilled unchanged from alkaline media. Hydration took place at a reasonable rate only above 150°, and preferably at 175—200°, with N-sodium hydroxide. No increase in ease of reaction could be found when more concentrated sodium hydroxide was used, but sodium carbonate less concentrated than 2N gave appreciable amounts of by-product. The catalytic power of the alkali is thus negligible, but its effect is to suppress side-reactions arising from rearrangement. The yield of diol under optimum conditions was 76%; as only 7% of high- and no low-boiling products were formed, the comparatively low yield may be due to difficulties of isolation.

The successful use of alkaline hydration to suppress side-reactions suggested its application to some other easily rearranged epoxides. This met with varying success. 2 : 3-Epoxy-2 : 4 : 4-trimethylpentane was almost entirely unchanged after 2 hr. with N-sodium hydroxide at 175°; increasing the time and temperature to 12 hr. at 200° gave 14% conversion into diol, but the rest of the epoxide was converted into 2 : 2 : 3 : 3-tetramethylbutanal and intermediate fractions. Increasing the concentration of the alkali to 5N under otherwise the same conditions partly suppressed the side-reactions but did not increase the amount of diol formed, and it was evident that alkaline hydration was of no value here. Styrene oxide was successfully hydrated to styrene glycol under similar conditions to those used for 1 : 2-epoxytrimethylpentane; this conversion has apparently not previously been achieved directly. The epoxide from α-methylstyrene, in the form of a purified oxidation product, was also converted into 2-phenylpropane-1 : 2-diol by this means.

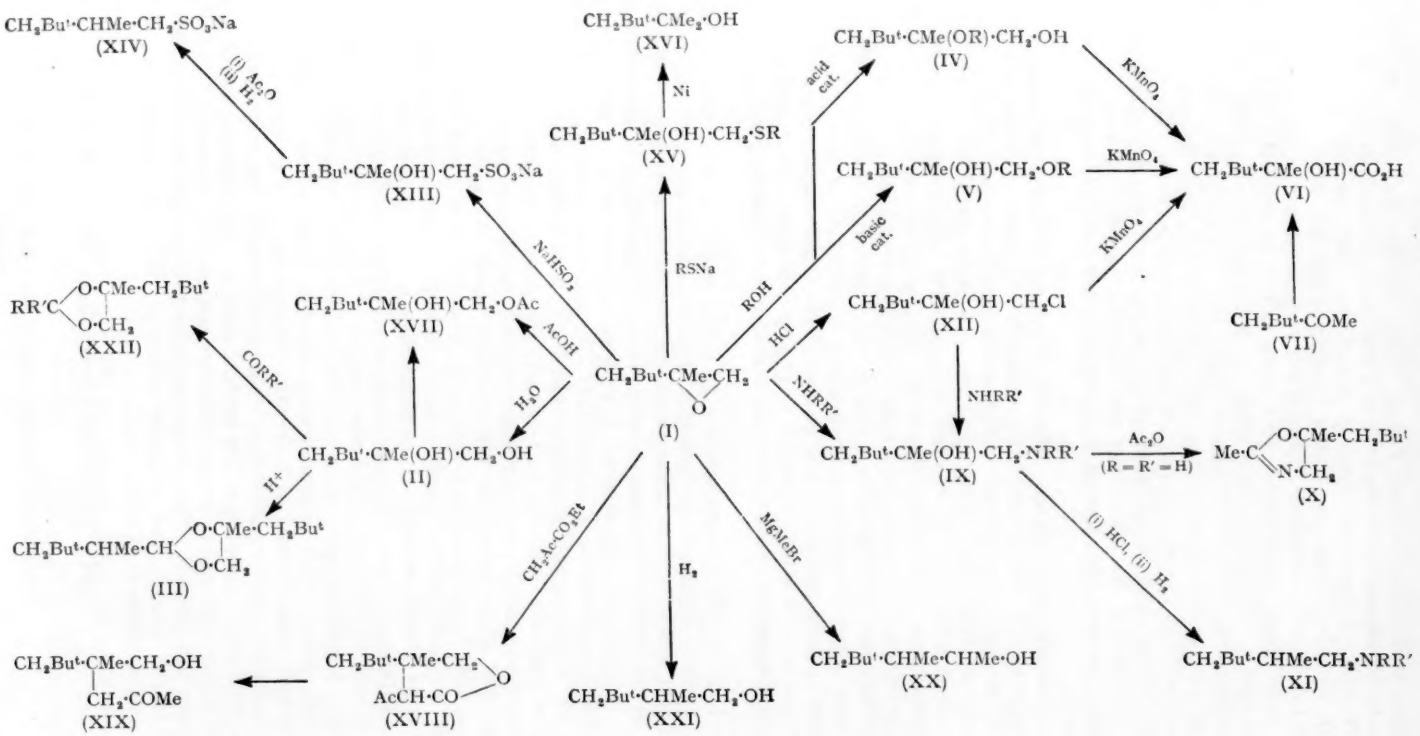
The 1 : 2-diol (II) is very sensitive to acids; water is eliminated on distillation at 15 mm. pressure, or simply on boiling in benzene solution, in either case with a trace of mineral acid, and it is quantitatively converted into an oil of somewhat higher b. p. This is without functional groups, and proved to be spectrographically identical with the " cyclic ether " obtained as a by-product from hydroxylation of 2 : 4 : 4-trimethylpent-1-ene (Byers and Hickinbottom, *J.*, 1948, 1328). Mugdan and Young (*J.*, 1949, 2995) showed this to be dihydro-4-methyl-4-*neo*pentyl-2-1′ : 3′ : 3′-trimethylbutyldioxole (III). Their method of synthesis, from the 1 : 2-diol (II) and trimethylpentanal (XXIV) in presence of a trace of mineral acid, was carried out on a very small scale, and is open to the criticism that the diol alone forms the same product under the same conditions. However, repetition with larger quantities, now easily available, gave a yield of 94% on diol plus aldehyde, so that there is no doubt that the aldehyde enters into the compound. Hence the structure postulated seems more reasonable than the dioxan structure advanced by Byers and Hickinbottom. The same cyclic acetal (III) is rapidly obtained if the glycol (II) is shaken with cold concentrated hydrochloric acid. Boiling the glycol with 6N-sulphuric acid gives a mixture of the cyclic acetal (III) and trimethylpentanal (XXIV).

In view of their ready formation from the diol, it seems that at least a part of the aldehyde and acetal formed as by-products during the acid hydration of the epoxide, except under the mildest possible conditions, and during hydroxylation of trimethylpentane, may have arisen from diol initially formed. The initial effect of acids on the diol (II) would presumably be to facilitate ionisation of the tertiary hydroxyl group, forming the ion (XXIII). This is also probably the intermediate in acid-catalysed ring opening of the epoxide, and evidently rearranges with considerable ease, by pinacolic change, to the aldehyde (XXIV):

$$\underset{\text{(II)}}{CH_2Bu^t\cdot CMe(OH)\cdot CH_2\cdot OH} \xrightarrow{H^+} \underset{\text{(XXIII)}}{CH_2Bu^t\cdot \overset{+}{C}Me\cdot CH_2\cdot OH} \longrightarrow$$

$$CH_2Bu^t\cdot CHMe\cdot \overset{+}{C}H\cdot OH \longrightarrow \underset{\text{(XXIV)}}{CH_2Bu^t\cdot CHMe\cdot CHO} + H^+$$

TABLE 1.


CH2But·CHMe·CH2·SO3Na (XIV)
(i) Ac2O (ii) H2
CH2But·CMe2·OH (XVI)
Ni
CH2But·CMe(OH)·CH2·SR (XV)
CH2But·CMe(OR)·CH2·OH (IV)
acid cat.
KMnO4
CH2But·CMe(OH)·CH2·SO3Na (XIII)
CH2But·CMe(OH)·CH2·OR (V)
KMnO4
CH2But·CMe(OH)·CO2H (VI)
NaHSO3
RSNa
ROH
basic cat.
KMnO4
RR'C(O·CMe·CH2But)(O·CH2) (XXII)
CH2But·CMe(OH)·CH2·OAc (XVII)
AcOH
CH2But·CMe(OH)·CH2Cl (XII)
HCl
CH2But·COMe (VII)
CORR'
H2O
CH2But·CMe·CH2 O (I)
NHRR'
NHRR'
CH2But·CMe(OH)·CH2·OH (II)
H+
CH2But·CMe(OH)·CH2·NRR' (IX)
Ac2O (R = R' = H)
Me·C(O·CMe·CH2But)=N·CH2 (X)
CH2But·CHMe·CH(O·CMe·CH2But)(O·CH2) (III)
CH2·AcCO2Et
H2
MgMeBr
(i) HCl, (ii) H2
CH2But·CMe(CH2·OH)·CH2·COMe (XIX)
CH2But·CMe·CH2 O / AcCH·CO (XVIII)
CH2But·CHMe·CH2·OH (XXI)
CH2But·CHMe·CHMe·OH (XX)
CH2But·CHMe·CH2·NRR' (XI)

This may then react, also under catalysis by acids, with unchanged diol to form the acetal (III).

Cyclic acetals (XXII) were also obtained from the glycol (II) with *cyclo*hexanone and benzaldehyde.

2 : 4 : 4-Trimethylpentane-2 : 3-diol is dehydrated much less readily by acids, and gives a complex product in which 2 : 4 : 4-trimethylpent-1-en-3-ol, 2 : 4 : 4-trimethylpentan-3-one, another aldehyde or ketone, and an unidentified cyclic ether or acetal were detected spectrographically.

Reaction with Alcohols.—From epoxide (I) and alcohols, either possible reaction product (IV) or (V) can be obtained according to whether acidic or basic catalysts are used. The isomeric products from any one alcohol could be distinguished by their physical and chemical properties. Comparison of their rates of esterification with acetyl chloride in pyridine–toluene showed that the adduct from acidic medium had the "abnormal" structure (IV), and that from basic medium the "normal" structure (V). Similar alteration in the character of the product by the nature of the catalyst has been observed and discussed before (cf. Swern, Billen, and Knight, *J. Amer. Chem. Soc.*, 1949, **71**, 1152, and refs. therein; Reeve and Sadle, *ibid.*, 1950, **72**, 1251), but this appears to be the first recorded case where either product could be obtained to the complete exclusion of the other.

The epoxide reacted rapidly and exothermally with an excess of lower primary alcohols in presence of a trace of sulphuric acid. The product was fairly complex, and besides about 30% of (IV) it contained unsaturated alcohol, aldehyde, acetal, and cylic acetal (III). It was clear that acid-catalysed rearrangement was a competing reaction, as in the case of acid hydration. None of the isomer (V) was detected in the product, and since (V; R = Et) was found to be quite stable to dilute alcoholic sulphuric acid, even at the b. p., it was certain that no appreciable amounts are formed.

Some search was made for a better yield of compounds of type (IV), which as primary alcohols were of some interest for esterification purposes. Various other catalysts were tried but only boron trifluoride, in the form of its ethyl ether complex, was better than sulphuric acid, giving a higher yield of a cleaner product. The highest yield (62%) was obtained with methanol; ethanol and *n*-butanol gave lower yields, but *iso*propanol gave, with sulphuric acid catalyst, none of the desired product (IV; R = Pr^i). Adducts were also prepared from various glycols and glycerol, which when employed in excess only reacted at one hydroxyl group—the more nucleophilic one in cases where they differed.

The epoxide did not react with an excess of ethanol and catalytic quantities of sodium ethoxide or sodium hydroxide at the atmospheric b. p. The reaction could be achieved smoothly either by increasing the temperature to 150° (autoclave) or by using a larger amount—1 mol.—of alkali at reflux temperature. Alcohols such as *n*-butanol with a higher b. p. could, however, be brought into reaction under reflux in presence of only small quantities of alkali. The necessary conditions can be generalised as 0·1—0·25 mol. of alkali at 150°, or an equimolar amount at 70—80°. The product was less complex than that from acid medium, and about 70% yields of various alkoxytrimethylpentanols (V) were obtained. *iso*Propanol, however, gave a very poor yield. Small yields of adducts were also obtained from phenol and 2-naphthol.

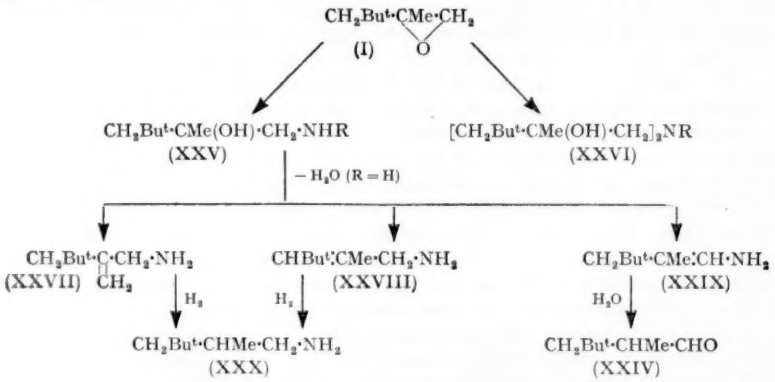
The "abnormal" adducts (IV) have higher b. p., density, and refractive index than their "normal" isomers (V). The lower members are oily liquids with the somewhat peppermint-like odour common to most di*iso*butylene derivatives. The glycol adducts are viscous liquids with an unpleasant acrid taste, sparingly soluble or insoluble in water, although the glycerol adduct is freely soluble. The compounds gave solid nitro- or dinitrobenzoates by which they could be characterised, although the tertiary alcohols were esterified with some difficulty. As already mentioned, this property was used to distinguish the "normal" adducts (V). However, after long boiling with acetic anhydride, (V; R = Et) gave an acetate in fairly good yield. Ineffective attempts were made to obtain an unsaturated ether by elimination of water from (V; R = Et). Distillation with iodine, etc., gave mainly trimethylpentanal; as just mentioned, boiling with acetic anhydride esterified the hydroxyl group, and heating with phthalic anhydride gave no

recognisable product except ethyl hydrogen phthalate. Treatment with concentrated hydrochloric acid gave an inseparable mixture of aldehyde and, apparently, unsaturated ether, but no chloro-compound.

Permanganate oxidation of (V; R = Et) gave the solid hydroxy-acid (VI), first described by Butlerov (*J. Russ. Phys. Chem. Soc.*, 1882, **14**, 201). The same acid was isolated from oxidation of (IV; R = Et). The structure of this acid was proved by synthesis from the cyanohydrin of 4 : 4-dimethylpentan-2-one (VII).

Attempts to combine ethanol with the epoxide without catalyst showed that no reaction took place below 200°, and above this temperature rearrangement to 2-*neo*pentylprop-2-en-1-ol took place (Part II, p. 2171). With methanol a small fraction, possibly (IV; R = Me), was obtained, but was not certainly identified.

Reaction with Ammonia and Amines.—1 : 2-Epoxy-2 : 4 : 4-trimethylpentane (I) combined with ammonia in concentrated aqueous or alcoholic solution at *ca.* 160° for 5 hr.; under less drastic conditions reaction was incomplete. Only two products were formed, 2-hydroxy-2 : 4 : 4-trimethylpentylamine (XXV; R = H) and di-(2-hydroxy-2 : 4 : 4-trimethylpentyl)amine (XXVI; R = H), in proportions varying with those of the reactants. None of the tertiary amine appeared to be formed; attempts to obtain this compound from (XXVI; R = H) and the epoxide failed, the starting materials being recovered unchanged after prolonged heating. Attempts to make the epoxide combine with ammonia in the gas phase were unsuccessful, the major products at above 290° being rearrangement products.

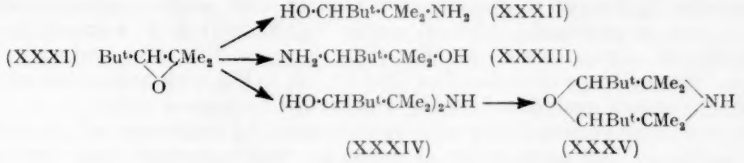


In early experiments on the reaction with ammonia a small fraction intermediate between the mono- and the di-hydroxy-amine was obtained. The existence of a separate compound was inferred from the refractive index, which was lower than those of the main products. Elementary analysis indicated a formula of approximately $C_{12}H_{27}ON$, but analysis of the 3 : 5-dinitrobenzoyl derivative showed it to be that of an amine $C_{16}H_{33}ON$. In later, larger-scale preparations this fraction did not appear; it may have originated from an impurity in the early batches of epoxide.

The structure of the monohydroxy-amine was expected, by analogy with similar cases described in the literature, to be 1-amino-2 : 4 : 4-trimethylpentan-2-ol (XXV; R = H). This was confirmed in two ways: (*a*) On refluxing amino-trimethylpentanol with concentrated hydrochloric acid, a poor yield of an unsaturated amine was obtained, together with a rather larger amount of 2 : 4 : 4-trimethylpentanal (XXIV). Spectroscopic evidence indicated that this unsaturated amine was a mixture of roughly equal parts of (XXVII) and (XXVIII). When it was hydrogenated, hydrogen equivalent to 1·0 double bond per molecule was absorbed, and the picrate of 2 : 4 : 4-trimethylpentylamine (XXX) was isolated from the product. The structure of (XXX) has been proved (see Part II, p. 2172). Further, dehydration to an unsaturated amine would not be possible if the monohydroxy-amine were 2-amino-2 : 4 : 4-trimethylpentan-1-ol. Trimethylpentanal may be supposed to have arisen through a vinylamine (XXIX). (*b*) As

described below, the monohydroxy-amine was prepared by interaction of 1-chloro-2 : 4 : 4-trimethylpentan-2-ol (XII) with methanolic ammonia.

The reaction of (XXV; R = H) with acetic anhydride did not afford the expected *N*-acetyl derivative. On distillation of the neutral portion of the product, some dehydration must have taken place, since one fraction was strongly basic. Analyses of this and its picrate left little doubt that it was substantially 4 : 5-dihydro-2 : 5-dimethyl-5-*neo*pentyloxazole (X), obtained by cyclic dehydration of the expected *N*-acetyl-hydroxy-amine.



Although 2 : 3-epoxy-2 : 4 : 4-trimethylpentane (XXXI) failed to react with ethanolic diethylamine, interaction with methanolic ammonia took place at 190° in 3—5 hr. A large excess of ammonia afforded a product corresponding to the monohydroxy-amine, probably a mixture of 2-amino-2 : 4 : 4-trimethylpentan-3-ol (XXXII) and 3-amino-2 : 4 : 4-trimethylpentan-2-ol (XXXIII). Since only one picrate and one hydrochloride were obtained it was assumed that one of these two components predominated. With restricted quantities of ammonia, a number of products was obtained. The lower-boiling fractions contained unchanged epoxide, a carbonyl compound (2 : 2 : 4-trimethylpentan-3-one, 2 : 2 : 3 : 3-tetramethylbutanal, or both), some (XXXII) or (XXXIII), and 2 : 4 : 4-trimethylpentane-2 : 3-diol. From the largest and highest-boiling fraction was obtained a homogeneous liquid, which elementary and functional-group analysis indicated to be, not the expected dihydroxy-amine (XXXIV), but a dehydration product thereof. All the evidence pointed to a morpholine structure, either (XXXV) or the isomeric structure with O and NH groups interchanged. Its infra-red spectrum confirmed the absence of hydroxyl groups and indicated the probable presence of an imino-group and an ether link. No fine structure characteristic of unsubstituted morpholine was displayed. This may be due to the heavy substitution about the ring. The yield of this material was 36% of theory.

In view of the failure of 1 : 2-epoxy-2 : 4 : 4-trimethylpentane (I) to form a triadduct with ammonia, it was of interest to find out whether a di- as well as a mono-adduct could be obtained from interaction with primary amines. Reaction products of both one and two molecules of epoxide (I) with methylamine were obtained; aniline, on the other hand, gave only a single product, the monoadduct. The epoxide (I) was allowed to react with both aqueous and alcoholic methylamine at *ca.* 180° in an autoclave. Two products, *N*-methyl-mono- (XXV; R = Me) and -di-(2-hydroxy-2 : 4 : 4-trimethyl-*n*-pentyl)amine (XXVI; R = Me) were produced in proportions which varied with those of the reactants. The second product solidified to a waxy solid, and all attempts to recrystallise it failed. Purification was eventually achieved by conversion into the hydrochloride or hydrobromide, and reconversion of the recrystallised salt into the amine. In this way, samples of base, m. p. 42—43° and 66°, respectively, were obtained. These differed little in their equivalent on titration. Examination of the infra-red spectrum showed the material of m. p. 66° to be the purest, but no trace of (XXVI; R = H) could be found to account for the impurity in specimens of lower m. p. This impurity is evidently a base of similar equivalent weight, but its exact nature has not been elucidated.

All attempts to quaternise the tertiary base (XXVI; R = Me) with methyl bromide or iodide failed; under drastic conditions some hydrobromide or hydriodide was formed. This behaviour is in contrast to the successful quaternisation of *N*-methyldi-(2 : 4 : 4-trimethylpentyl)amine (see Part II, p. 2173). The epoxide (I) failed to react with triethylamine.

Interaction of the epoxide (I) with ethanolic diethylamine and aqueous dimethylamine

at 180° for several hours afforded high yields of *NN*-diethyl- (IX; R = R′ = Et) and *NN*-dimethyl-2-hydroxy-2 : 4 : 4-trimethylpentylamine (IX; R = R′ = Me), respectively; both readily formed methiodides. The structure of the product with diethylamine as (IX) and not the isomeric 2-diethylamino-1-hydroxy-compound follows from its synthesis from 1-chloro-2 : 4 : 4-trimethylpentan-2-ol (XII) (see below). The structures of the other products of addition of amines to the epoxide have not been rigidly proved. They are based on analogy with the above instances and with similar reactions of unsymmetrical epoxides reported in the literature.

The epoxide (I) reacted in the expected manner with aniline, methylaniline, and morpholine, each in methanolic solution, giving *N*-(2-hydroxy-2 : 4 : 4-trimethylpentyl)-aniline (XXV; R = Ph), -*N*-methylaniline (IX; R = Ph, R′ = Me), and -morpholine, respectively. No evidence of a diadduct (XXVI; R = Ph) with aniline was observed. The morpholine adduct quaternised readily with methyl bromide or iodide.

The non-formation of more highly substituted amines and quaternary salts is attributed to steric hindrance. An examination of molecular models suggests that, whereas the compounds described above have unstrained molecules, the *NN*-di-(2-hydroxy-2 : 4 : 4-trimethylpentyl)-*NN*-dimethylammonium cation would be too strained to exist. The molecules of *NN*-di-(2-hydroxy-2 : 4 : 4-trimethylpentyl)aniline and tri-(2-hydroxy-2 : 4 : 4-trimethylpentyl)amine, and the *N*-2-hydroxy-2 : 4 : 4-trimethylpentyl-*NNN*-trimethylammonium cation, although they could exist without or with only slight strain, would be extremely cramped and rigid; they are doubtless very difficult to form, especially as the reaction transition states may be strained.

Reaction with Acids, Salts, etc.—The epoxide (I) did not appear to react with acetic acid in the absence of a catalyst. In the presence of a trace of sulphuric acid, a rapid and exothermic reaction took place, but only a poor yield of impure product was obtained; this did, however, appear to be the expected glycol monoacetate. In presence of sodium acetate (1 mole) in acetic acid at the b. p., the glycol monoacetate was formed very slowly but with less side-reaction, and was obtained pure; it was identical with the ester formed by treating the diol (II) with 1 mole of acetic anhydride, and so was identified as 2-hydroxy-2 : 4 : 4-trimethylpentyl acetate (XVII). Surprisingly, in presence of boron trifluoride the product was mainly the aldehyde (XXIV).

The epoxide reacted readily with formic acid without catalyst. The product appeared to be the glycol monoformate, but was not obtained pure. The product from interaction with acetyl chloride in boiling carbon tetrachloride was very complex, but appeared to include trimethylpentenyl acetate, chlorotrimethylpentane, and chlorotrimethylpentyl acetate. As mentioned in Part II (p. 2170), with acetic anhydride and a trace of sulphuric acid, (I) gave almost exclusively 2 : 4 : 4-trimethylpentylidene diacetate.

The quantitative aspects of the reaction between the epoxide and ethereal hydrogen chloride are discussed in Part I (p. 2163). On the preparative scale, a very vigorous reaction set in when the epoxide (I) was added to a small excess of hydrogen chloride in ether. About 60—70% of the theoretical amount of hydrogen chloride was absorbed, but the conversion into chlorohydrin was poor and seldom exceeded 25%. A second chlorine-containing compound was also formed, together with large quantities of 2 : 4 : 4-trimethylpentanal (XXIV). These two products had boiling points very close to one another and were not readily separable by distillation. The yield of chlorohydrin was very much reduced when the epoxide was treated with concentrated hydrochloric acid. Correspondingly greater quantities of aldehyde (XXIV) were formed.

Only one of the two possible chlorohydrin isomers was isolated. This may be due either to instability of the second isomer or to the absence of any addition to the epoxide in that direction. The chlorohydrin was homogeneous on distillation, and its reactions gave rise to only one series of products. The chlorohydrin was somewhat unstable and tended to lose hydrogen chloride rather readily except in presence of weak bases. The chlorine atom could be replaced by hydroxy-, amino-, and diethylamino-groups by reaction in Carius tubes with methanolic potassium acetate, ammonia, and diethylamine, respectively. The product in each case was identified with the material produced from epoxide (I) by hydration and interaction with ammonia and diethylamine respectively

(see above). In the last two cases, no indications of the presence of any 2-amino-1-hydroxy-compounds, derived from the isomeric chlorohydrin, were noted. This establishes the fact that additions of ammonia, diethylamine, and hydrogen chloride to the ring of the epoxide (I) all take place in the same direction.

The chlorohydrin was readily dehydrated with anhydrous oxalic acid. An unsaturated chloro-compound, presumably 1-chloro-2 : 4 : 4-trimethylpent-2-ene or an isomer thereof, was obtained. The fact that dehydration could be brought about easily to give an unsaturated chloro-compound constitutes strong evidence that the chlorohydrin is correctly formulated as the 1-chloro-2-hydroxy-compound (XII) and not the 2-chloro-1-hydroxy-isomer. In the latter case, dehydration could only have been accomplished if extensive degradation of the molecule had taken place. This in turn affords further proof of the correctness of the structures of the reaction products of the epoxide (I) with ammonia and diethylamine. An unsaturated chloro-compound obtained by the reaction of chlorine or hypochlorous acid with di*iso*butylene has been described by Umnowa (*J. Russ. Phys. Chem. Soc.*, 1910, **42**, 1536), and this might be expected to have the same or a similar constitution.

The chlorine atom in the unsaturated chloro-compound was unaffected by cold 0·1N-sodium hydroxide. Hydrogenation in the presence of Adams's catalyst caused simultaneous removal of the chlorine atom. On the other hand, all attempts to remove the chlorine atom in the original chlorohydrin by similar means failed. By oxidation of the chlorohydrin with hot alkaline permanganate, α-hydroxy-αγγ-trimethylvaleric acid (VI) was obtained.

It did not appear possible to obtain sulphuric esters from the epoxide (I) and sulphuric acid of any concentration, since the very dilute acid gives diol (II) (see above) and higher concentrations cause rearrangement to the aldehyde (XXIV) (Part II, p. 2170). Similarly, it was found that phosphoric acid of concentrations from 85% to 100%, or containing dissolved phosphoric oxide, and even phosphoric oxide alone, acted entirely as rearrangement catalysts, and no phosphorus-containing product could be obtained.

A reaction took place between the epoxide and phosphorus oxychloride in dimethyl- or diethyl-aniline, but the product was mainly aldehyde, and the higher-boiling material contained only a little combined phosphorus or chlorine. In carbon tetrachloride solution, both phosphorus oxychloride and sulphuryl chloride gave low-boiling products—probably a mixture of chlorohydrin and chloro-trimethylpentene—which contained chlorine but no phosphorus or sulphur.

Epoxide (I) reacted with 10% aqueous sodium sulphite when heated in an autoclave to 150°. A slow reaction took place at the atmospheric b. p. Sodium 2-hydroxy-2 : 4 : 4-trimethylpentane-1-sulphonate (XIII) crystallised as a monohydrate from the aqueous layer in a yield of 55%. From the organic layer which remained, 2 : 4 : 4-trimethylpentane-1 : 2-diol (II) (10%) was isolated, together with 4 : 4-dimethylpentan-2-one and possibly some 2 : 3-epoxide (an impurity in the original epoxide).

When the hydroxy-sulphonate (XIII) was refluxed with acetic anhydride for 15 min., dehydration took place and a mixture of sodium 2 : 4 : 4-trimethylpentene-1-sulphonates was produced. The presence of the double bond was readily established by reaction with bromine. Preparation of an *S*-benzylthiuronium salt confirmed that this product was a mixture of the possible unsaturated sulphonates, but only one derivative was isolated pure.

The ease of dehydration of the hydroxy-sulphonate indicates that the hydroxy-group is attached to a tertiary carbon atom. Had addition of sodium sulphite to the epoxide taken place in the opposite direction to give sodium 1-hydroxy-2 : 4 : 4-trimethylpentane-2-sulphonate, dehydration to an unsaturated sulphonate would have been impossible.

Hydrogenation of the mixed unsaturated sulphonates readily proceeded in aqueous solution in presence of Adams's catalyst. About 80% of the theoretical amount of hydrogen was absorbed. The sodium 2 : 4 : 4-trimethylpentane-1-sulphonate (XIV) monohydrate thus obtained yielded a homogeneous *S*-benzylthiuronium salt.

The epoxide (I) was heated with an equimolecular amount of aqueous potassium cyanide in an autoclave at 140°. Part of the epoxide was still unchanged after 5 hr. The non-acidic products were complex. Two fractions were identified as the diol (II) and dihydroxy-amine (XXVI; R = H), the latter in considerable quantity. Another fraction

had a nitrile-like odour; analysis showed that it was not the expected 2-hydroxy-2 : 4 : 4-trimethylpentyl cyanide (XXXVI), but a vinyl cyanide, probably (XXXVII) formed by dehydration of the initial product :

$$(I) \longrightarrow \underset{(XXXVI)}{CH_2Bu^t\cdot CMe(OH)\cdot CH_2\cdot CN} \longrightarrow \underset{(XXXVII)}{CH_2Bu^t\cdot CMe{:}CH\cdot CN}$$

This inference was supported by the infra-red absorption spectrum. A fourth high-boiling fraction was not identified. Its microanalysis agreed approximately with the empirical formula $C_{16}H_{33}ON$. Examination of the infra-red spectrum did not shed any light upon its structure.

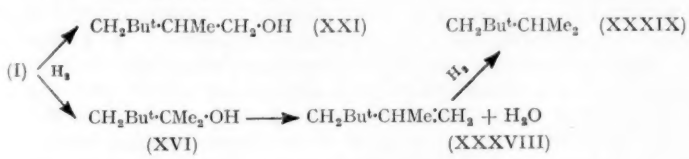
It was evident that this reaction had been unduly complicated by the high temperature and strongly alkaline conditions used. Thus, the diol formed is almost certainly due to direct hydration of the epoxide, and it is probable that the dihydroxy-amine arose from interaction of the epoxide with a limited quantity of ammonia formed by alkaline hydrolysis of some of the nitrile.

Miscellaneous Reactions.—Sodium methyl sulphide reacted exothermally with the epoxide (I) at room temperature. The expected product, 1-methylthio-2 : 4 : 4-trimethylpentan-2-ol (XV; R = Me), was obtained in moderate yield as a colourless liquid of characteristic odour. The structure was proved by hydrogenolysis of the methylthio-group with Raney nickel. The 2 : 4 : 4-trimethylpentan-2-ol (XVI) thus obtained was identified by comparison of its physical properties and spectrum with those of an authentic specimen synthesised by Ritter's method (*J. Amer. Chem. Soc.*, 1948, **70**, 4253) from 2 : 4 : 4-trimethylpent-1-ene and methyl cyanide in 92% sulphuric acid. 1-Benzylthio-2 : 4 : 4-trimethylpentan-2-ol (XV; R = CH_2Ph) was isolated in 75% yield from interaction of the epoxide (I) and sodium benzyl sulphide in boiling aqueous ethanol. The structure assigned to the product is based on analogy with that of the methylthio-compound.

The epoxide (I) reacted with methylmagnesium iodide to give a mixture of C_9 alcohols, containing about 50% of 3 : 5 : 5-trimethylhexan-2-ol (XX) derived from the aldehyde (XXIV), the remainder being presumably the 3-ol. The alcohol (XX) was synthesised from the aldehyde (XXIV) and methylmagnesium iodide.

Condensation of the epoxide (I) with ethyl sodioacetoacetate was achieved under rather drastic conditions (dioxan solution, 150° for 5 hr.). The product appeared to be a mixture of the expected initial product, $CH_2Bu^t\cdot CMe(OH)\cdot CH_2\cdot CHAc\cdot CO_2Et$, and the lactone (XVIII). Attempted ketonic hydrolysis of this gave a product, also apparently a mixture, but which yielded a dinitrophenylhydrazone giving an analysis in agreement with that calculated for the derivative of the expected hydroxy-ketone (XIX).

The hydrogenation of the epoxide (I) was investigated briefly as a possible alternative route from the epoxide to 2 : 4 : 4-trimethylpentan-1-ol (XXI). In the liquid phase at 110—120° over Raney nickel, the products were (XXI) (50—60%), water, 2 : 4 : 4-trimethylpent-1-ene (XXXVIII), and 2 : 2 : 4-trimethylpentane (XXXIX). These results are accounted for on the assumption that the epoxide ring broke in either possible direction, and that the tertiary alcohol (XVI) so formed was dehydrated to (XXXVIII), which was then in part hydrogenated to (XXXIX) :



A somewhat similar product was obtained by vapour-phase hydrogenation over a nickel–pumice catalyst at 200°. In view of the relatively poor yields of trimethylpentanol obtained by direct hydrogenation as compared with the indirect route (see Part II, p. 2172), this method was not pursued further.

Experimental

Hydration of Epoxides.—Acid hydration. (i) 1 : 2-Epoxy-2 : 4 : 4-trimethylpentane (I) (320 g.) was stirred for 5 hr. with 0·1N-sulphuric acid (1 l.). After a preliminary run, the separated aqueous layer was recycled from one run to the next. The reaction was slightly exothermic, and the temperature was controlled to below 35°. The product was separated by warming the mixture to 35° to liquefy the glycol and removing the top liquid layer; this was then washed free from acid with N-sodium hydroxide, and again warmed to 30—35° to separate the phases. The resultant 2 : 4 : 4-trimethylpentane-1 : 2-diol (II) was purified from unchanged epoxide and by-products by distillation (b. p. 105—110°/10 mm.), a product, m. p. 55—57°, being obtained. The yield was about 238 g. per run; some 50 g. of unchanged epoxide, trimethylpentanal, and an intermediate fraction (unsaturated alcohol) were obtained. On a small scale it was preferable to extract the diol (II) with ether.

Table 2 shows the effect of the nature and concentration of the acid upon the yield (%) of (*a*) unchanged epoxide and aldehyde, (*b*) intermediate fraction, b. p. 50—107°/10 mm., (*c*) glycol (II), and (*d*) condensation products, b. p. 112—130°/10 mm.

Table 2.

Reagent	Time, hr.	(*a*)	(*b*)	(*c*)	(*d*)	Reagent	Time, hr.	(*a*)	(*b*)	(*c*)	(*d*)
N-H_2SO_4	3	6	18	40	0	0·02N-H_2SO_4.....	5	26	9	43	0
0·2N-H_2SO_4	5	0	25	51	0	0·01N-H_2SO_4.....	10	40	3	33	0
0·1N-H_2SO_4	5·25	4	16	71	0	0·1N-HCl	5	0	27	30	32
0·05N-H_2SO_4	5	8	12	61	0	0·01N-HNO_3 ...	5	0	6	75	0

0·1N-Sulphuric acid diluted with half its volume of ethanol gave a 75% yield of glycol after 5 hr.; addition of ethanol has no obvious advantage.

(ii) 2 : 3-Epoxy-2 : 4 : 4-trimethylpentane (XXXI) (32 g.) was shaken with 0·1N-sulphuric acid (100 ml.) at room temperature for 12 hr., by which time the organic phase was partially crystalline. After extraction and washing there were obtained 23·2 g. (64%) of 2 : 4 : 4-trimethylpentane-2 : 3-diol, b. p. 90—92°/10 mm., together with 3·5 g., b. p. 20—48°/10 mm. (? unchanged epoxide), and 4·4 g. of an intermediate fraction.

Alkaline hydration of (I). (i) The epoxide (I) (50 ml.) was refluxed for 66 hr. with N-sodium hydroxide (200 ml.), and was recovered substantially unchanged. Only a trace of glycol was formed. The epoxide distils rapidly in steam.

(ii) Epoxide (I) (64 g.) and N-sodium hydroxide (200 ml.) was heated to 200° for 2·5 hr. in a Baskerville–Lindsay autoclave with reciprocating stirrer. The organic product was separated (warming to 35° being necessary for liquefaction) and distilled without further treatment; the alkali was recycled. The combined product from three such runs gave no low-boiling material except water, 167 g. (76%) of diol (II), and 14 g. of residue (7%). A similar yield was obtained with 2N-sodium carbonate at 175° (3 hr.); 10% of epoxide was unchanged.

Alkaline hydration of some other epoxides. 2 : 3-Epoxy-2 : 4 : 4-trimethylpentane (XXXI) (64 g.) and N-sodium hydroxide (200 ml.) were heated in the same autoclave at 200° for 12 hr. The product was extracted with ether. Distillation gave 19·5 g. of 2 : 2 : 3 : 3-tetramethylbutanal, b. p. 47—50°/10 mm. (solidified), 14·3 g. of an intermediate fraction, and 9·9 g. (14%) of 2 : 3-diol, b. p. 90—94°/10 mm. Repetition with 5N-sodium hydroxide (10 hr.) gave 7·4 g. (10%) of 2 : 3-diol, together with 33·1 g. of apparently unchanged epoxide and 12·0 g. of intermediate fraction.

Styrene oxide (6 g.) was heated with N-sodium hydroxide (10 ml.) in a Carius tube to 175° for 3 hr. The product was ether-extracted, and afforded 1-phenylethane-1 : 2-diol (2·2 g.), b. p. 155—165°/12 mm., m. p. 62—64° from benzene, and much high-boiling and undistillable material.

A mixture of 1 : 2-epoxy-2-phenylpropane (55%) and, mainly, acetophenone was made by Dr. W. Webster, of this Department, by oxidisng α-methylstyrene by the method of B.P. 682,067. This fraction, b. p. 79·5—81°/10 mm. (16·5 g.), was heated with N-sodium hydroxide (70 ml.) for 4·5 hr. at 200°. Low-boiling fractions (6·3 g.), b. p. 82—114°/10 mm., were obtained from the product, followed by 2-phenylpropane-1 : 2-diol (1·7 g.), b. p. 144—150°/10 mm., m. p. 44—46° from benzene–light petroleum (Danilow and Venus-Danilowa, *Ber.*,1927, **60**, 1061, give m. p. 44°, b. p. 149—150°/11 mm.).

Miscellaneous methods. (i) Epoxide (I) (32 g.), water (100 ml.), and ethanol (20 ml.) were refluxed for 3 hr. The initial pH of the aqueous layer was 3—4. The product was extracted with ether, which gave material (9·1 g.), b. p. below 100°/10 mm. (largely 70—80°/10 mm.), and diol (II) (12·9 g., 35%).

(ii) The epoxide (I) (50 g.) was refluxed for 12 hr. with 25% acetic acid (200 ml.). A large light fraction, presumably aldehyde, was steam-distilled out; the residue gave further quantities of low-boiling material, and a liquid (16·7 g.), b. p. 112—134°/10 mm., presumably (III).

Properties and Reactions of 2 : 4 : 4-*Trimethylpentane*-1 : 2-*diol* (II) *and* -2 : 3-*diol*.—The solubility of each diol in water at 20° is 3%. Under water the 1 : 2-diol (II) melts at 36°, and two liquid phases are formed, the lower consisting of diol containing 20% of water. Above 36° the solubility decreases and later increases with temperature. The 2 : 3-diol melts under water at 43°, and the lower phase thus formed contains 10% of water. The 1 : 2-diol (II) is very soluble (>50%) in methanol and ethanol at room temperature, less so in acetone and ethyl acetate, sparingly soluble in benzene, carbon tetrachloride, toluene, ethylene dichloride, and *cyclo*hexanol, and only slightly soluble (>1%) in cold paraffin hydrocarbons, although readily soluble when hot.

The following vapour-pressure values for the 1 : 2-diol (II) were found by means of an ebulliometer:

V. p.	0·3	20	40	60	100	200	400	760 mm.
Temp. ...	20°	118·7°	134·3°	143·8°	157·1°	175·1°	196·8°	219·8° (decomp.)

The diol (II) (20 g.) was refluxed in benzene solution (150 ml.), and a drop of sulphuric acid added. Water was immediately evolved as an azeotrope and was removed in a Dean and Stark trap. The washed benzene solution then yielded quantitatively dihydro-4-methyl-4-*neo*pentyl-2-1′ : 3′ : 3′-trimethylbutyldioxole (III), b. p. 132°/10 mm., n_D^{20} 1·4408. Its identity with synthetic material (see below) was confirmed by infra-red spectrum. The same product resulted when the diol was distilled at 15 mm. with a trace of sulphuric acid.

The diol (II) (10 g.) was refluxed for 1 hr. with N-sulphuric acid (100 ml.). After being made alkaline, the product was isolated, and consisted of trimethylpentanal (3·5 g.), b. p. 42—54°/18 mm., n_D^{20} 1·4150, and the acetal (III) (4·5 g.), b. p. 130—140°/18 mm., n_D^{20} 1·4382.

The glycol (II) (10 g.) was refluxed for 1 hr. with 50% (by vol.) acetic acid (80 ml.) and then worked up as in the last experiment to yield low-boiling material (1·6 g.), probably aldehyde, and unchanged glycol (6·6 g.).

The diol (II) (10 g.) was shaken with concentrated hydrochloric acid at room temperature, whereupon it liquefied immediately. Next morning the product was extracted with ether, washed with aqueous sodium hydroxide, and distilled to give the cyclic acetal (III) (6·4 g.) and low-boiling material (1·4 g.).

The glycol (II) (29 g.) and trimethylpentanal (XXIV) (26 g., 1 mol.) were dissolved in benzene refluxing in a Dean and Stark apparatus. When a drop of sulphuric acid was added, an exothermic reaction ensued, and water rapidly came off as an azeotrope; 3·1 ml. were collected (calc., 3·6 ml.). When the distillate was clear, the benzene solution was washed with sodium hydroxide solution, dried, and distilled over potassium carbonate. The resultant cyclic acetal (III) (49 g., 94%) had b. p. 132°/10 mm., n_D^{20} 1·4409 (Found: C, 74·5; H, 13·0. Calc. for $C_{16}H_{32}O_2$: C, 75·0; H, 12·5%).

The glycol (II) (29·2 g.), *cyclo*hexanone (16·6 g.), and phosphoric acid (1 drop) were azeotropically dehydrated as above. The product (19·3 g.), *dihydro*-4-*methyl*-4-neo*pentyl*cyclo*hexane*spiro-2-*dioxole*, had b. p. 124°/10 mm., n_D^{20} 1·4562 (Found: C, 73·8; H, 11·5. $C_{14}H_{26}O_2$ requires C, 73·9; H, 12·0%). The diol (II) and benzaldehyde were similarly condensed to give *dihydro*-4-*methyl*-4-neo*pentyl*-2-*phenyldioxole* (XXII; R = Ph, R′ = H), b. p. 155—157°/10 mm., n_D^{20} 1·4961 (Found: C, 77·1; H, 9·7. $C_{15}H_{22}O_2$ requires C, 77·4; H, 9·5%).

Distillation of 2 : 4 : 4-trimethylpentane-2 : 3-diol with sulphuric acid gave two fractions, b. p. *ca.* 150° and 240—260°. Spectroscopic examination showed that the latter was an unidentified cyclic ether, and the former was a mixture of 2 : 4 : 4-trimethylpent-1-en-3-ol (~30%), 2 : 4 : 4-trimethylpentan-3-one (~20%), (?) 2 : 2 : 3 : 3-tetramethylbutanal (~30%), and unchanged diol (~5%).

The 1 : 2-diol (II) (29 g.), acetic anhydride (20 g.), and pyridine (18 g.) were warmed on the steam-bath for an hour. Working up in the normal way gave 13·5 g. of the monoacetate (XVII), b. p. 108·5—110°/10 mm., n_D^{20} 1·4413, spectroscopically identical with that obtained from the epoxide and acetic acid (see below). The diacetate, prepared as described by Hickinbottom (*J.*, 1948, 1333), had b. p. 120°/12 mm., n_D^{20} 1·4341.

Reaction with Alcohols.—Products from acid catalysis. (*a*) With ethanol. The epoxide (I) (100 g.) was slowly added to a mechanically stirred solution of sulphuric acid (1·2 g.) in ethanol (500 ml.), at such a rate that the temperature did not rise above 45°. Next morning, the catalyst was neutralised (to pH 9) with sodium hydroxide solution, and the excess of ethanol

was distilled off. The residue was taken up in ether, washed with water, and submitted to fractional distillation. The fraction, b. p. 94—97°/12 mm. (34·2 g.), was identified as 2-*ethoxy*-2 : 4 : 4-*trimethylpentan*-1-*ol* (IV; R = Et), but it contained some 8% of (presumably) 2 : 4 : 4-trimethylpentanal diethyl acetal, detected by hydroxylamine titration. Much lower- and higher-boiling material were also obtained, but despite repeated attempts no pure compound was isolated therefrom. From titration results, the presence of 2-*neo*pentylprop-2-en-1-ol and the aldehyde acetal was inferred. A better product, b. p. 92—93°/10 mm., n_D^{20} 1·4403, d_4^{20} 0·8994, was obtained from a similar reaction employing 64 g. of epoxide, 250 ml. of ethanol, and 2 ml. of boron trifluoride–ethyl ether complex. This was judged to be free from acetal and from (V; R = Et) by spectroscopic examination, and gave a satisfactory analysis [Found: C, 68·6; H, 12·7; OEt, 25·6; active H (Zerewitinov), 0·59; (Smith and Bryant), 0·54. $C_{10}H_{21}O(OH)$ requires C, 69·0; H, 12·7; OEt, 25·8; active H, 0·58%]. It formed a 3 : 5-*dinitrobenzoate*, m. p. 89—90° (dinitrobenzoates were recrystallised from ethanol except where otherwise stated) (Found: C, 55·5; H, 6·54. $C_{17}H_{24}O_7N_2$ requires C, 55·4; H, 6·56%).

The effect of various catalysts may be summarised by tabulating the yield of (IV; R = Et) (Table 3).

TABLE 3.

Catalyst	Catalyst, mol.	Temp.	Yield, %	Catalyst	Catalyst, mol.	Temp.	Yield, %
H_2SO_4	0·058	20—40°	25	Zeocarb-215 ...	0·03 (equiv.)	78°	0
,, ...	0·013	,,	27	HCl	0·006	,,	0
,, ...	0·0026	,,	29	BF_3–Et_2O	0·03	20—40°	37
,, ...	0·013	−4° to −1°	13	$AlCl_3$	0·01	,,	3
H_3PO_4	0·01	78°	39	$ZnCl_2$	0·075	78°	0
p-$C_6H_4Me{\cdot}SO_3H$	0·01	,,	23				

(*b*) With methanol. Addition of epoxide (1 kg.) to methanol (4 l.) containing boron trifluoride–ether complex (32 ml.) and working up as for ethanol gave 777 g. (62%) of 2-*methoxy*-2 : 4 : 4-*trimethylpentan*-1-*ol* (IV; R = Me), b. p. 90—93·5°/12 mm., d_4^{20} 0·9129, n_D^{20} 1·4433 [Found: C, 67·1; H, 12·7; OMe, 19·3; active H (Zerewitinov), 0·70; (Smith and Bryant), 0·59. $C_9H_{19}O(OH)$ requires C, 67·5; H, 12·6; OMe, 19·4; active H, 0·63%]. Its 3 : 5-*dinitrobenzoate* had m. p. 74—75° (Found: C, 54·2; H, 6·0. $C_{16}H_{22}O_7N_2$ requires C, 54·2; H, 6·0%).

An attempt was made to distil the product directly, in the hope that the boron trifluoride would appear as a separate fraction and be recovered. Complete decomposition occurred, however. As an alternative to neutralisation with alkali, the trifluoride could be removed by refluxing the solution for ½ hr. with an excess of sodium fluoride and filtering. This method has the advantage that the recovered sodium borofluoride can be reconverted into boron trifluoride, and also that the solution is then free from inorganic material and requires no further washing.

Sulphuric acid being used as catalyst, a 47% yield of the same product was obtained. No (V; R = Me) could be detected spectroscopically in the product.

(*c*) With higher alcohols. *iso*Propanol, with sulphuric acid as catalyst, failed to give any of the desired product.

From *n*-butanol, with sulphuric acid catalyst, was obtained 2-*butoxy*-2 : 4 : 4-*trimethylpentan*-1-*ol* (IV; R = Bu^n), b. p. 114—119°/10 mm., d_4^{20} 0·8802, n_D^{20} 1·4408 (Found: C, 71·1; H, 13·0; OBu, 38·2. $C_{12}H_{26}O_2$ requires C, 71·2; H, 13·0; OBu, 36·1%) (yield 29%). The 3 : 5-*dinitrobenzoate* had m. p. 66—67° (Found: C, 57·5; H, 6·9. $C_{19}H_{28}O_7N_2$ requires C, 57·6; H, 7·1%).

(*d*) With glycols. The epoxide (128 g.) was added slowly with mechanical stirring to ethylene glycol (150 g.) containing boron trifluoride–ether complex (1·5 ml.), the temperature being controlled below 45°. Sufficient sodium hydroxide, dissolved in a little water, was added to neutralise all the catalyst, and unchanged glycol and low-boiling by-products were distilled off up to 120°/10 mm. The residue was taken up in ether, washed, and dried, and on distillation gave a main product (79·4 g., 42%), b. p. 112—116°/0·5 mm., n_D^{20} 1·4597. Analysis showed clearly that it was 2-2′-*hydroxyethoxy*-2 : 4 : 4-*trimethylpentan*-1-*ol* (IV; R = $HO{\cdot}CH_2{\cdot}CH_2$) [Found: C, 63·4; H, 11·9; active H (Zerewitinov), 0·86; (Smith and Bryant), 0·94. $C_{10}H_{20}O(OH)_2$ requires C, 63·1; H, 11·6; active H, 1·05%]. It formed a *bis*-3 : 5-*dinitrobenzoate*, m. p. 107—109° from acetone (Found: C, 49·8; H, 4·63; N, 9·75. $C_{24}H_{26}O_{13}N_4$ requires C, 49·9; H, 4·53; N, 9·7%). In another experiment, the unchanged glycol was washed out with water in order that the by-products could be examined. These proved to be similar (unsaturated alcohol, acetal) to those from reaction with ethanol.

Attempted esterification of the product with $\alpha\gamma\gamma$-trimethylvaleric acid by azeotropically

removing water with toluene in presence of a little toluene-*p*-sulphonic acid as catalyst gave a mixed product of unexpectedly low b. p. Presumably fission at the C–O–C bond had occurred. The *bis-αγγ-trimethylvalerate*, b. p. 160—164°/2 μ, n_D^{20} 1·4472, was obtained in 82% yield from the glycol adduct (19·0 g.) and the acid chloride (32·5 g.) in pyridine (19·0 g.), cautiously mixed with cooling and kept overnight at room temperature (Found : equiv., 223. $C_{26}H_{50}O_5$ requires equiv., 221).

A similar reaction between the epoxide and propane-1 : 3-diol afforded 2-3′-*hydroxypropoxy*-2 : 4 : 4-*trimethylpentan*-1-*ol* (IV; R = HO·[CH_2]$_3$) (39%), b. p. 134°/0·5 mm., n_D^{20} 1·4623 (Found : C, 65·1; H, 11·2. $C_{11}H_{24}O_3$ requires C, 64·6; H, 11·8%). The 3 : 5-dinitrobenzoate could not be crystallised, but the *di*-p-*nitrobenzoate* recrystallised from acetone–ethanol and had m. p. 65—67° (Found : C, 59·6; H, 5·9; N, 5·82, 6·13. $C_{25}H_{30}O_9N_2$ requires C, 59·7; H, 6·1; N, 5·6%).

2-Methylpentane-2 : 4-diol gave a product in which one hydroxyl group was unreactive and presumably tertiary; it was therefore the expected 2-(3-*hydroxy*-1 : 3-*dimethylbutoxy*)-2 : 4 : 4-*trimethylpentan*-1-*ol* (IV; R = HO·CMe_2·CH_2·CHMe). The product had b. p. 113—115°/0·1 mm., n_D^{20} 1·4548 [Found : C, 68·5; H, 12·3; active H (Zerewitinov), 0·72; (Smith and Bryant), 0·415. $C_{14}H_{28}O(OH)_2$ requires C, 68·4; H, 12·3; active, H, 0·82%]. The yield was only 11%.

(*e*) With glycerol. Epoxide (128 g.) was added slowly to mechanically stirred glycerol (300 g.) and boron trifluoride–ether (2 ml.) with cooling. On addition of dilute sodium hydroxide, the mixture remained homogeneous, but triple extraction with ether removed 2-(2 : 3-dihydroxypropoxy)-2 : 4 : 4-trimethylpentan-1-ol (IV; R = OH·CH_2·CH(OH)·CH_2) (68 g., 31%), b. p. 154—158°/0·3 mm., n_D^{20} 1·4688, a very viscous liquid. This did not give good analytical figures and the dinitrobenzoate could not be obtained as a solid, but the *tri*-p-*nitrobenzoate* crystallised from acetone–ethanol and had m. p. 128—130° (Found : C, 57·6; H, 4·8; N, 6·27. $C_{32}H_{33}O_{13}N_3$ requires C, 57·6; H, 5·0; N, 6·3%).

Products from basic catalysis. (*a*) With ethanol. Preliminary experiments in which the epoxide was refluxed with ethanol containing up to 0·05N concentration of sodium ethoxide showed that no reaction took place thus.

Sodium (23 g., 1 mole) was dissolved in ethanol (500 ml.), and epoxide (128 g., 1 mole) added. No immediate reaction was apparent. After the solution had refluxed for 3 hr., most of the epoxide was found by titration to have been consumed. Most of the alcohol was evaporated off, and the residue washed with water, taken up in ether, and distilled. The main product thus obtained (118·0 g., 68%) had b. p. 79°/16 mm., d_4^{20} 0·8693, n_D^{20} 1·4277, and although it showed one hydroxyl group (Zerewitinov), it failed to react appreciably under the normal conditions of a Smith and Bryant titration, or with benzoyl chloride in diethylaniline within 1½ hr. at 60°. Its infra-red spectrum showed a tertiary hydroxyl group, and the absence of a detectable amount of (IV; R = Et). It was therefore 1-*ethoxy*-2 : 4 : 4-*trimethylpentan*-2-*ol* (V; R = Et) [Found : C, 69·1; H, 13·2; OEt, 24·0; active H (Zerewitinov), 0·57. $C_{10}H_{21}O(OH)$ requires C, 69·0; H, 12·7; OEt, 25·8; active H, 0·58%]. It gave, with some difficulty, a 3 : 5-*dinitrobenzoate*, m. p. 48—50° (Found : C, 55·5; H, 6·5. $C_{17}H_{24}O_7N_2$ requires C, 55·4; H, 6·6%), and an *acetate*, b. p. 92°/10 mm., n_D^{20} 1·4263 (Found : C, 66·8; H, 11·2. $C_{12}H_{24}O_3$ requires C, 66·6; H, 11·2%).

The same compound was obtained in 61—66% yield by substituting the equivalent amount of sodium hydroxide for sodium ethoxide, or by heating the epoxide and ethanol with sodium ethoxide (0·1 mol.) or hydroxide (0·25 mol.) to 150° for 5 hr. The last method afforded a very slow conversion at 100°.

(*b*) With other alcohols. 1-*Methoxy*-2 : 4 : 4-*trimethylpentan*-2-*ol* (V; R = Me), b. p. 65—66°/10 mm., d_4^{20} 0·8802, n_D^{20} 1·4294, was prepared in 51% yield by using sodium methoxide (1 mol.) in methanol at reflux temperature [Found : C, 67·6; H, 13·1; OMe, 19·5; active H, 0·55. $C_9H_{19}O(OH)$ requires C, 67·5; H, 12·6; OMe, 19·4; active H, 0·63%]. Its 3 : 5-*dinitrobenzoate* had m. p. 68° (Found : C, 54·2; H, 6·5. $C_{16}H_{22}O_7N_2$ requires C, 54·2; H, 6·0%). The product was spectroscopically free from (IV; R = Me).

A similar reaction with *iso*propanol gave only a 7·5% yield of the 1-iso*propoxy*-analogue (V; R = *iso*-C_3H_7); a better yield (20%) was obtained with 0·1 mol. of sodium *iso*propoxide at 150° (5·5 hr.; autoclave). The compound had b. p. 79—83°/10 mm., d_4^{20} 0·8608, n_D^{20} 1·4272 [Found : C, 70·5; H, 13·0; active H (Zerewitinov), 0·57. $C_{11}H_{23}O(OH)$ requires C, 70·2; H, 12·8; active H, 0·54%]. The dinitrobenzoate could not be satisfactorily purified.

Heating of the epoxide with *n*-butanol and sodium hydroxide (1 mol.) under reflux (3 hr.) afforded the 1-*butoxy*-compound (V; R = *n*-C_4H_9), b. p. 100—104°/10 mm., d_4^{20} 0·8668, n_D^{20}

1·4335, in 68% yield [Found: C, 71·5; H, 13·0; active H (Zerewitinov), 0·62. $C_{12}H_{25}O(OH)$ requires C, 71·2; H, 13·0; active H, 0·50%]. Slightly smaller yields were obtained on using 0·25 mol. of sodium hydroxide either under reflux or at 150° in an autoclave (3 hr.).

By heating the epoxide (64·0 g.) with dodecan-1-ol (200 g.; from fractionation of commercial lauryl alcohol) and sodium hydroxide (10·0 g.) at 175° for 2 hr. in an autoclave, a small yield of the 1-*dodecyloxy*-compound (V; R = *n*-$C_{12}H_{25}$), b. p. 168—180°/0·5 mm., n_D^{20} 1·4474, was obtained (Found: C, 76·6; H, 13·3. $C_{20}H_{42}O_2$ requires C, 76·4; H, 13·3%).

(*c*) With ethylene glycol. A mixture of epoxide (128 g.), ethylene glycol (150 g.), and sodium hydroxide (8 g.) was heated in a stirred autoclave at 175° for 3 hr. Water was added, and the product extracted into ether. Fractionation afforded 1-2′-*hydroxyethoxy*-2 : 4 : 4-*trimethylpentan*-2-*ol* (V; R = $OH{\cdot}CH_2{\cdot}CH_2$) (86·5 g.; 46%), b. p. 94—100°/0·3 mm., n_D^{20} 1·4541. This was not quite pure, but the structure assigned was confirmed by the detection of one reactive and one unreactive hydroxyl group [Found: C, 63·8; H, 11·0; active H (Zerewitinov), 0·95; (Smith and Bryant), 0·53. $C_{10}H_{20}O(OH)_2$ requires C, 63·1; H, 11·6; active H, 1·05%].

(*d*) With phenols. Phenol (47 g.) was dissolved in a solution of sodium hydroxide (20 g.) in ethanol (40 ml.) and water (50 ml.), epoxide (64 g.) added thereto, and the whole refluxed for 8 hr. After dilution with water the product was extracted with ether, giving 2 : 4 : 4-*trimethyl*-1-*phenoxypentan*-2-*ol* (V; R = Ph) (45 g., 40%), b. p. 148—153°/10 mm., n_D^{20} 1·4993 [Found: C, 75·6; H, 10·0; active H (Zerewitinov), 0·42. $C_{14}H_{21}O(OH)$ requires C, 75·6; H, 10·0; active H, 0·45%]. It formed a 3 : 5-*dinitrobenzoate*, m. p. 88—90° (Found: C, 60·0; H, 5·8; N, 6·82. $C_{21}H_{14}O_7N_2$ requires C, 60·5; H, 5·8; N, 6·72%). The reaction was slow, as some unchanged reagents were found on working-up.

A similar procedure with 2-naphthol gave the 1-2′-*naphthoxy*-analogue (V; R = 2-$C_{10}H_7$), b. p. 136—140°/0·003 mm. This solidified and could be recrystallised from chilled light petroleum (b. p. 40—60°) in asbestos-like needles, m. p. 46—47° (Found: C, 78·9; H, 8·5. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·9%). The reaction was exceedingly slow, only a 19% yield being obtained after 24 hr. of refluxing; reaction at 150° in an autoclave gave a very impure product.

Reactions of Ethoxytrimethylpentanols.—Both (IV) and (V; R = Et) were unchanged by 3 hours' refluxing with ethanol containing a little sulphuric acid. When (V; R = Et) was distilled over a little iodine, not much water was eliminated. The distillate, b. p. 145—148°, was mainly (87% by titration) 2 : 4 : 4-trimethylpentanal. The product from similar treatment of (IV; R = Et) was qualitatively similar.

Compound (V; R = Et) (39 g.) was shaken for 3 hr. with concentrated hydrochloric acid (100 ml.). The washed organic phase, recovered by means of ether, yielded materials (15·3 g.), b. p. 40—42°/10 mm., n_D^{20} 1·4191, and (1·8 g.), b. p. 108—114°/10 mm., and a residue (1·4 g.). The first fraction appeared by titration to consist of aldehyde (XXIV) (41%) and an ethoxytrimethylpentene (55%).

Compound (V; R = Et) (18 g.) was heated on a steam-bath with potassium permanganate (32 g.) and sodium hydroxide (40 g.) in water (500 ml.). After removal of manganese dioxide and neutral organic product, the solution was acidified and extracted with ether, which removed α-hydroxy-αγγ-trimethylvaleric acid (VI) (1·8 g.), m. p. 107—108° (undepressed by a synthetic sample, see below) [Found: C, 60·3; H, 10·1; active H (Zerewitinov), 1·22%; OEt, nil; equiv., 157. Calc. for $C_7H_{14}(OH)(CO_2H)$: C, 60·0; H, 10·1; active H, 1·26%; equiv., 160]. The same acid was obtained in similar yield by oxidation of (IV; R = Et).

4 : 4-Dimethylpentan-2-one (VII) (57 g.) in methanol (300 ml.) was added to potassium cyanide (40 g.) in water (100 ml.), and sulphuric acid (30 g.) in water (100 ml.) was added dropwise with stirring. After 2 hr. the mixture was diluted with water (2 vol.). An ethereal extract yielded much unchanged ketone, and a fraction (5 g.), b. p. 110—117°/20 mm., n_D^{20} 1·432. This was presumably the cyanohydrin. This material (2 g.) was refluxed with concentrated hydrochloric acid for 2 hr., and acidic products were isolated in ether, yielding (VI) (0·34 g.), m. p. 106° undepressed by admixture with the specimen obtained as above or from the chlorhydrin.

Reaction with Ammonia and Amines.—With ammonia. (*a*) The epoxide (I) (256 g., 2·0 moles) and aqueous ammonia (1·5 l.; *d* 0·88; approx. 27 moles) were heated with stirring in a steel autoclave to 190° for 5 hr. When cool, the amines were extracted twice into chloroform, and the combined extracts were washed with a small amount of water, dried (Na_2SO_4), and distilled. After the solvent, two main fractions, b. p. 85—95°/18 mm. and 170—180°/15 mm., were obtained. On occasions, a small intermediate fraction, b. p. 120—140°/14 mm., n_D^{20} 1·4535, was also obtained. By redistillation of the first main fraction, 2-*hydroxy*-2 : 4 : 4-*trimethylpentylamine* (XXV; R = H), b. p. 87—88°/14 mm., n_D^{20} 1·4580, d_{20}^{20} 0·8991, K_b 4·5 × 10^{-5}, was obtained (Found: C, 66·1; H, 13·4; N, 9·6%; equiv., 144. $C_8H_{19}ON$ requires C, 66·1; H,

13·2; N, 9·6%; equiv., 145). The *picrate* (unless stated, picrates were recrystallised from ethanol or aqueous ethanol) formed orange plates, m. p. 151—152° (Found: N, 14·8. $C_8H_{19}ON,C_6H_3O_7N_3$ requires N, 15·0%); the *hydrochloride* crystallised in plates, m. p. 183°, from ethanol–ether (Found: C, 52·8; H, 10·6; N, 7·7. $C_8H_{19}ON,HCl$ requires C, 52·9; H, 11·1; H, 7·7%). The second main fraction yielded *di-(2-hydroxy-2 : 4 : 4-trimethylpentyl)amine* (XXVI; R = H), b. p. 175—180°/14 mm., b. p. 130—132°/1 mm., d_{20}^{20} 0·9088, n_D^{20} 1·4619 (Found: C, 70·6; H, 13·1; N, 5·3. $C_{16}H_{35}O_2N$ requires C, 70·3; H, 12·9; N, 5·1%). The *picrate* crystallised in long prisms, m. p. 154—155° (Found: C, 52·7; H, 7·4; N, 11·2. $C_{16}H_{35}O_2N,C_6H_3O_7N_3$ requires C, 52·6; H, 7·6; N, 11·1%). The *sulphate* crystallised in prisms, m. p. 228—229°, from water containing a little ethanol (Found: N, 4·4. $2C_{16}H_{35}O_2N,H_2SO_4$ requires N, 4·3%). The *carbonate* crystallised in laths, m. p. 204°, from ethanol–ether (Found: C, 61·0; H, 11·5. $C_{16}H_{35}O_2N,H_2CO_3$ requires C, 60·9; H, 11·1%).

(*b*) The epoxide (I) (512 g., 4 moles) and aqueous ammonia (1050 ml., *d* 0·88; 20 moles) were heated with stirring in the autoclave to 158—160° for 5 hr. A maximum pressure of 31 atm. was reached. After refluxing to remove the excess of ammonia, sodium chloride (250 g.) was added, and the mixture extracted twice with toluene (500, 100 ml.). On fractionation of the combined extracts, the toluene–water azeotrope distilled out first, followed by toluene, (XXV; R = H) (313 g., 54%), and (XXVI; R = H) (166 g., 30%).

(*c*) The epoxide (I) (128 g., 1 mole) and 3·5N-ethanolic ammonia (300 ml., 1·05 moles) were heated together in an autoclave at 180° for 4 hr. The product was distilled directly. After removal of ethanol and a trace of aminotrimethylpentanol, the secondary amine was obtained in 66% yield.

The intermediate fraction mentioned above was produced occasionally from earlier batches of epoxide. It could be further purified by a second distillation, and then had b. p. 129—130°/14 mm., n_D^{20} 1·4535 (Found: C, 71·6; H, 13·4; N, 7·2; active H, 0·51. $C_{12}H_{27}ON$ requires C, 71·6; H, 13·4; N, 7·0; active H, 0·49%). A 3 : 5-*dinitrobenzoyl* derivative was prepared, which after repeated recrystallisation from aqueous ethanol and then light petroleum, had m. p. 131—132° (Found: C, 60·9; H, 7·8; N, 9·5. $C_{22}H_{35}O_6N_3$ requires C, 60·4; H, 8·0; N, 9·6%).

The effect upon the yield of mono- and di-hydroxy-amines of varying the molar proportions of epoxide to ammonia may be summarised :

Ratio NH_3 : (I)	1·15	4·25	5·0	6·75	15	67
Yield (%) of (XXV; R = H)	9	51·5	54	57	63	63
,, (XXVI; R = H)	71·5	34	30	26	9	trace

The hydroxy-amine (XXV; R = H) (20 g.) was refluxed with concentrated hydrochloric acid (100 ml.) for 2 hr. An oily layer rapidly separated. This was extracted with ether, washed, dried, and distilled, yielding 2 : 4 : 4-trimethylpentanal (XXIV), b. p. 37—40°/13 mm., n_D^{20} 1·4139 (6·9 g., 39%; 95% pure), identified as its dinitrophenylhydrazone, m. p. 143°. The acidic layer was basified with sodium hydroxide, and the oil which separated was isolated in ether. Distillation afforded an unsaturated *amine* (XXVII or XXVIII) (18%), b. p. 51—53°/13 mm., n_D^{20} 1·4488 (Found: C, 75·4; H, 13·5; N, 10·8%; equiv., 130. $C_8H_{17}N$ requires C, 75·5; H, 13·4; N, 11·0%; equiv., 127). By microhydrogenation of the amine (250 mg.) in ethanol over Adams's catalyst, hydrogen equivalent to 1·0 double bond per mole was absorbed. Picric acid was added to the filtered solution, and 2 : 4 : 4-trimethylpentylamine picrate separated, m. p. 190° after recrystallisation (cf. Part II, p. 2178).

The hydroxy-amine (XXV; R = H) (16·5 g.), sodium hydrogen carbonate (20 g.), water (200 ml.), and ether (150 ml.) were stirred and cooled in ice whilst benzoyl chloride (17 g., 20% excess) was added dropwise. A white solid began to separate, but redissolved on addition of chloroform. The solvent layer was extracted with dilute sodium hydroxide, then with sulphuric acid, and dried, and concentrated. The residue was triturated with ether and recrystallised from chloroform–light petroleum (b. p. 100—120°) to give laths (23 g., 92%) of 1-*benzamido*-2 : 4 : 4-*trimethylpentan*-2-*ol*, m. p. 103—105° (Found: C, 71·2; H, 9·4. $C_{15}H_{23}O_2N$ requires C, 72·3; H, 9·3%).

The hydroxy-amine (XXV; R = H) (22 g.) was treated with acetic anhydride (22 g.) and pyridine (20 ml.); much heat was evolved. After 1 hr., the mixture was poured into water, and the neutral product isolated in ether. Distillation gave two small fractions. The first, b. p. 70—76°/14 mm. (3 g.), n_D^{20} 1·4422, appeared to be impure 4 : 5-*dihydro*-2 : 5-*dimethyl*-5-*neopentyloxazole* (X) (Found: C, 69·6; H, 11·1; N, 7·7%; equiv., 180. $C_{10}H_{19}ON$ requires C, 70·9; H, 11·3; N, 8·3%; equiv., 169). It gave a *picrate*, m. p. 126° (Found: C, 48·1; H, 5·5; N, 13·8. $C_{10}H_{19}ON,C_6H_3O_7N_3$ requires C, 48·2; H, 5·6; N, 14·1%). The second fraction,

b. p. 135—140°/14 mm., n_D^{20} 1·4695 (2·5 g.), was non-basic, but gave a similar analysis (Found : C, 68·8; H, 11·0; N, 7·4%).

With methylamine. A mixture of epoxide (I) (128 g., 1 mole), 33% ethanolic methylamine (70 g., 0·75 mole), and ethanol (250 ml.) was heated in the autoclave for 5 hr. at 180°. After removal of ethanol and excess of methylamine by distillation, major fractions of b. p. 79—90°/14 mm. and 160—180°/15 mm. were obtained. The former on redistillation gave 2-*hydroxy*-2 : 4 : 4 : N-*tetramethylpentylamine* (XXV; R = Me) (0·24 mole), b. p. 82°/14 mm., n_D^{20} 1·4461, K_b 8 × 10^{-4} (Found : C, 67·5; H, 13·1; N, 9·0. $C_9H_{21}ON$ requires C, 67·9; H, 13·3; N, 8·8%). The *picrate* formed yellow prisms, m. p. 129—130° (Found : N, 14·4. $C_9H_{21}ON,C_6H_3O_7N_3$ requires N, 14·4%). The second fraction slowly solidified. The waxy solid, *N*-methyldi-(2-hydroxy-2 : 4 : 4-trimethylpentyl)amine (XXVI; R = Me), could not be recrystallised. The *hydrochloride*, prepared in ether, after several recrystallisations from ethanol–ether had a somewhat indefinite m. p., 169—172° (Found : C, 63·3; H, 11·9; N, 4·1. $C_{17}H_{37}O_2N$,HCl requires C, 63·0; H, 11·8; N, 4·3%).

An aqueous suspension of the hydrochloride was basified, and the amine extracted with ether. After being dried, the extract was concentrated, leaving the *amine* (XXVI; R = Me) as a solid, m. p. 42—43°; sublimation at 1 mm. did not raise the m. p. (Found : C, 71·0; H, 12·6; N, 5·0%; equiv., 283. $C_{17}H_{37}O_2N$ requires C, 71·0; H, 13·0; N, 4·9%; equiv., 287). The amine was very readily soluble in all organic solvents. In a similar way, the *hydrobromide*, prepared by adding concentrated hydrobromic acid to an ethanolic solution of the crude amine, and recrystallised from aqueous ethanol to m. p. 198° (Found : C, 55·7; H, 10·1; N, 4·1. $C_{17}H_{37}O_2N$,HBr requires C, 55·4; H, 10·4; N, 3·8%), gave a regenerated amine of m. p. 66° (Found : C, 70·9; H, 12·8%; equiv., 285).

With diethylamine. Diethylamine (320 ml., 3·1 moles), ethanol (300 ml.), and epoxide (I) (256 g., 2 moles) were heated in a stainless-steel autoclave at 160° for 5 hr. with stirring. Distillation of the product afforded NN-*diethyl*-2-*hydroxy*-2 : 4 : 4-*trimethylpentylamine* (IX; R = R′ = Et), b. p. 95—96°/15 mm., 220°/756 mm., n_D^{20} 1·4401, K_b 5 × 10^{-4} [Found : C, 71·5; H, 13·6; N, 6·7; active H, 0·45%; equiv., 196. $C_{12}H_{26}N(OH)$ requires C, 71·6; H, 13·5; N, 6·9; active H, 0·50%; equiv., 201]. The *picrate* formed lemon-yellow cubes, m. p. 105° (Found : C, 50·6; H, 6·7; N, 13·2. $C_{12}H_{27}ON,C_6H_3O_7N_3$ requires C, 50·2; H, 7·0; N, 13·0%). Incomplete reaction took place in 3 hr. at 140°, some 25% of epoxide being unchanged. In the absence of ethanol, reaction only occurred to the extent of about 5%.

The amine (IX; R = R′ = Et) (150 g.) was quaternised by heating it with methyl iodide (150 g.) in methanol (500 ml.) in an autoclave at 120° for 5 hr. Evaporation left the *methiodide* (170 g., 66%), which crystallised from ethanol–ether in irregular aggregates, m. p. 147° (Found : C, 45·7; H, 8·6. $C_{13}H_{30}ONI$ requires C, 45·5; H, 8·8%). This salt was extractable into chloroform from aqueous alkaline solution. It was also prepared in poor yield by refluxing the amine with excess of dimethyl sulphate in ethanol for 5 hr., evaporating the ethanol, adding aqueous sodium hydroxide and iodide in excess, and extracting the quaternary iodide with chloroform, from which it was readily isolated.

Methyl bromide (4 g.), the amine (5 g.), and ethyl acetate (25 g.) were heated to 130° for 5 hr. in a Carius tube. The product formed two layers, the lower and more viscous of which dissolved in acetone and subsequently deposited crystals (4 g., 55%). After recrystallisation from acetone containing a little ether, the *methobromide* had m. p. 124—126° (Found : Br, 26·7. $C_{13}H_{30}ONBr$ requires Br, 27·0%). The bromide was converted into the iodide with sodium iodide in boiling acetone. The hot solution was filtered, and the corresponding quaternary iodide crystallised out on cooling. Its m. p. was 144° alone and when mixed with the pure iodide described above. The quaternary bromide was not extracted into chloroform from an alkaline aqueous solution.

With dimethylamine. Epoxide (I) (128 g., 1 mole) was heated in a 1-l. stainless-steel stirred autoclave with 33% aqueous dimethylamine (200 g., 1·5 mole) at 180° for 4 hr. The oily layer was extracted into chloroform, and the extract was dried, concentrated, and distilled, yielding 2-*hydroxy*-2 : 4 : 4 : N : N-*pentamethylpentylamine* (IX; R = R′ = Me), b. p. 77—78°/14 mm., n_D^{20} 1·4370 (76%) (Found : C, 69·8; H, 13·4; N, 7·6. $C_{10}H_{23}ON$ requires C, 69·3; H, 13·4; N, 8·1%). The *picrate* crystallised from ethanol in yellow rhombs, m. p. 128° (Found : C, 48·1; H, 6·5; N, 14·1. $C_{10}H_{23}ON,C_6H_3O_7N_3$ requires C, 47·8; H, 6·5; N, 13·9%). The *methiodide* had m. p. 129—130° after recrystallisation from ethanol–ether (Found : N, 4·0; I, 40·7. $C_{11}H_{26}ONI$ requires N, 4·4; I, 40·3%).

With aniline. Aniline (64 g., 0·69 mole), epoxide (I) (64 g., 0·5 mole), and methanol (200 ml.) were heated in a stainless-steel autoclave at 170—180° for 5 hr. The product was distilled, and

after removal of methanol and excess of aniline, a fraction, b. p. 150—195°/10 mm. (mainly 185—190°) (54 g.), was obtained. Little residue remained. The high-boiling fraction largely solidified and was triturated under light petroleum (b. p. 40—60°). Recrystallisation from the same solvent afforded needles of N-2-*hydroxy*-2 : 4 : 4-*trimethylpentylaniline* (XXV; R = Ph), m. p. 68° (Found : C, 76·0; H, 10·4; N, 6·4. $C_{14}H_{23}ON$ requires C, 76·0; H, 10·5; N, 6·3%). The *picrate* crystallised from aqueous ethanol in orange plates, m. p. 134—135° (Found : C, 53·7; H, 5·8; N, 12·0. $C_{14}H_{23}ON,C_6H_3O_7N_3$ requires C, 53·3; H, 5·8; N, 12·4%).

With methylaniline. Redistilled methylaniline (17·1 g., 0·16 mole), epoxide (I) (17·1 g., 0·134 mole), and methanol (35 ml.) were heated together at 170—180° for 3·5 hr. in a stainless-steel autoclave. By distillation of the product, a main fraction, b. p. 164—166°/10 mm. (11·7 g., 38%), was obtained, which on redistillation afforded N-(2-*hydroxy*-2 : 4 : 4-*trimethylpentyl*)-N-*methylaniline* (IX; R = Ph, R′ = Me), b. p. 165—167°/10 mm., n_D^{20} 1·5282 (Found : C, 76·7; H, 10·6; N, 6·1. $C_{15}H_{25}ON$ requires C, 76·5; H, 10·7; N, 5·9%).

With morpholine. Epoxide (I) (64 g., 0·5 mole), morpholine (64 g., 0·73 mole), and methanol (250 ml.) similarly afforded 4-(2-*hydroxy*-2 : 4 : 4-*trimethylpentyl*)*morpholine*, b. p. 125—126°/12 mm., n_D^{20} 1·4633 (Found : C, 66·6; H, 11·6; N, 6·7%; equiv., 212. $C_{12}H_{25}O_2N$ requires C, 66·9; H, 11·7; N, 6·5%; equiv., 215). The *picrate* crystallised from methanol in yellow prisms, m. p. 158° (Found : C, 48·9; H, 6·4; N, 12·9. $C_{12}H_{25}O_2N,C_6H_3O_7N_3$ requires C, 48·7; H, 6·3; N, 12·6%). The *methiodide*, m. p. 108—110° (Found : C, 44·0; H, 7·6; N, 3·6. $C_{13}H_{28}O_2NI$ requires C, 43·7; H, 7·9; N, 3·9%), was recrystallised from acetone–ethyl acetate (2 : 3). The *methobromide* formed plates, m. p. 161—164° (Found : C, 50·6; H, 9·2; N, 4·3; Br, 25·7. $C_{13}H_{28}O_2NBr$ requires C, 50·3; H, 9·1; N, 4·5; Br, 25·8%), from acetone containing a little methanol.

Interaction of Ammonia with 2 : 3-*Epoxy*-2 : 4 : 4-*trimethylpentane.*—(*a*) The epoxide (XXXI) (64 g., 0·5 mole) and aqueous ammonia (500 ml.; *d* 0·88; 9·0 mole) were stirred and heated at 190° for 3 hr. in a stainless-steel autoclave. The product was extracted with ether, washed with a little water, dried, and fractionated. A main fraction of b. p. 76—81°/15 mm. (15%) (Found : equiv., 146) was obtained. Redistillation afforded a series of fractions, ranging from b. p. 73°/12 mm., n_D^{20} 1·4534, to b. p. 78°/12 mm., n_D^{20} 1·4569, which appeared to correspond to mixtures of 2-amino-2 : 4 : 4-trimethylpentan-3-ol (XXXII) and 3-amino-2 : 4 : 4-trimethylpentan-2-ol (XXXIII) (Found : C, 66·3; H, 13·1; N, 9·4. Calc. for $C_8H_{19}ON$: C, 66·1; H, 13·2; N, 9·6%). A *picrate*, prepared from a middle cut, had m. p. 188—191° after recrystallisation (Found : C, 45·0; H, 6·0; N, 14·6. $C_8H_{19}ON,C_6H_3O_7N_3$ requires C, 44·9; H, 5·9; N, 15·0%). From the lowest-boiling fractions, the same picrate was obtained, but in a less pure state and with a much lower initial m. p. The *hydrochloride*, after recrystallisation from ethanol–ether, had m. p. 222° (Found : C, 53·0; H, 10·8; N, 7·7. $C_8H_{19}ON,HCl$ requires C, 52·9; H, 11·1; N, 7·7%).

(*b*) The epoxide (XXXI) (64 g., 0·5 mole), aqueous ammonia (110 ml.; *d* 0·88; 1·8 mole), and water (150 ml.) were heated as before to 180—200° for 5 hr. The product was extracted into chloroform, washed, dried, and fractionated. After removal of a little unchanged epoxide, some ketonic material, mono-hydroxy-amines, and 2 : 4 : 4-trimethylpentane-2 : 3-diol, a main fraction, b. p. 125—128°/14 mm. (Found: equiv., 253), was obtained. Redistillation afforded (probably) 2 : 6-*di*-tert.-*butyl*-3 : 3 : 5 : 5-*tetramethylmorpholine* (XXXV), b. p. 127—129°/12 mm., n_D^{20} 1·4577 [Found : C, 75·2; H, 13·0; N, 5·8; active H, 0·34%; equiv., 253. $C_{16}H_{32}O(NH)$ requires C, 75·2; H, 13·0; N, 5·5; active H, 0·39; equiv., 255]. No hydroxyl groups were detectable by the Smith and Bryant method. The basic group was difficult to acetylate, for only 80% had reacted after 30 minutes' refluxing with acetic anhydride. The *picrate* formed bright yellow crystals, m. p. 191° (Found: C, 54·7; H, 7·5; N, 11·7. $C_{16}H_{33}ON,C_6H_3O_7N_3$ requires C, 54·5; H, 7·5; N, 11·6%).

Reaction with Acids, Salts, etc.—With acetic acid. (*a*) The epoxide (I) (30 g.) was added during 2—3 min. to glacial acetic acid (200 ml.) containing sulphuric acid (1 g.). The sulphuric acid was neutralised with an excess of powdered anhydrous sodium acetate, and after filtration, most of the acetic acid was removed under reduced pressure. The residue was partitioned between ether and water, and the alkali-washed ethereal layer distilled. Two fractions of main product were obtained : b. p. 80—110°/15 mm. (3·5 g.; n_D^{20} 1·4359) and 110—125° (mostly 113°)/15 mm. (3·4 g.; n_D^{20} 1·4395). By hydrolysis these gave equivalents of 219 and 216, respectively (calc., 188).

(*b*) Epoxide (I) (64 g.), anhydrous sodium acetate (41 g.), and acetic acid (500 ml.) were refluxed for 10 hr. The sodium acetate remained apparently unchanged. After being worked up as in (*a*), the product on distillation gave unidentified material (7·8 g.), b. p. 71—78°/10 mm.,

n_D^{20} 1·4341, and 2-*hydroxy*-2 : 4 : 4-*trimethylpentyl acetate* (12·7 g.), b. p. 107°/12 mm., n_D^{20} 1·4392 [Found : C, 63·6; H, 10·6; active H (Zerewitinov), 0·51; (Smith and Bryant), 0·30%; equiv., 192. $C_{10}H_{19}O_2(OH)$ requires C, 63·8; H, 10·7; active H, 0·54%; equiv., 188]. The infra-red spectrum proved it to be identical with the synthetic glycol monoacetate (XVII), and showed a non-primary hydroxyl group.

(*c*) The epoxide (I) (64 g.) was added slowly to acetic acid (250 ml.) containing boron trifluoride–ether complex (2 ml.); the reaction was exothermic. After removal of most of the acetic acid under reduced pressure, the residue was washed with sodium hydroxide solution and extracted with ether. The main product (34·1 g.; b. p. 35—44°/10 mm.) was largely aldehyde (XXIV); only 4·9 g. of a fraction, b. p. 103—110°/10 mm., were obtained.

With acetyl chloride. Epoxide (I) (64 g.) was added slowly to boiling acetyl chloride (40 g.) and carbon tetrachloride (250 ml.), and the mixture distilled. The product was complex and no pure compound was isolated. From analytical data, the presence of the following was inferred : unchanged acetyl chloride (12·4 g.), together with solvent in fractions of b. p. <100°/760 mm.; chlorotrimethylpentene, b. p. <131°/760 mm.; trimethylpentenyl acetate, b. p. 34—82°/12 mm.; trimethylchloropentyl acetate, b. p. 82—105°/12 mm.

With hydrogen chloride. Epoxide (I) (32 g., 0·25 mole) was added to 3·5N-ethereal hydrogen chloride (80 ml., 0·275 mole) at 0°, and after an exothermic reaction had taken place the mixture was left at 0° for 2 hr. The excess of hydrogen chloride was removed by ice-cold water, and the ether layer was dried ($MgSO_4$ and MgO) and distilled. The fraction, b. p. 65—75°/14 mm. (10·2 g., 25%), was redistilled, giving 1-*chloro*-2 : 4 : 4-*trimethylpentan*-2-*ol* (XII), b. p. 70—71°/13 mm., n_D^{20} 1·4519 [Found : C, 58·5; H, 10·7; Cl, 22·8; active H, 0·56. $C_8H_{16}Cl(OH)$ requires C, 58·3; H, 10·4; Cl, 21·5; active H, 0·61%]. In addition, a large fraction, b. p. 148—152°/760 mm., was obtained, which contained trimethylpentanal (*ca.* 60%), identified as its dinitrophenylhydrazone, together with a chlorine-containing compound, the halogen of which was stable to cold aqueous alkali.

Titration of the chlorohydrin (XII) in ethanol with aqueous sodium hydroxide to phenolphthalein resulted in slow absorption of alkali equivalent to the whole of the chlorine present.

The chlorohydrin (XII) (10 g.), potassium acetate (8 g.), and methanol (20 ml.) were heated in a Carius tube at 140° for 16 hr. The product was concentrated and poured into water, and the oily layer isolated in ether. Distillation gave 2 : 4 : 4-trimethylpentane-1 : 2-diol (II) (2·7 g.), b. p. 100—107°/13 mm., m. p. 60° undepressed by authentic material.

The chlorohydrin (XII) (3·5 g.), diethylamine (6 ml.), and methanol (5 ml.) were heated in a Carius tube at 160° for 3 hr. The contents of the tube were diluted with ether, and diethylamine hydrochloride, m. p. 222°, was filtered off. The filtrate was concentrated, and the basic portion isolated in ether. From this, *NN*-diethyl-2-hydroxy-2 : 4 : 4-trimethylpentylamine (IX; R = R′ = Et) (1·4 g.), b. p. 90—95°/13 mm., n_D^{20} 1·4409, was obtained. Its identity with the material obtained as above was confirmed by preparation of the picrate, m. p. and mixed m. p. 104°.

The chlorohydrin (XII) (8 g.) and 9N-methanolic ammonia (45 g.) were heated in a Carius tube at 140° for 19 hr. The product was concentrated, the residue dissolved in chloroform, and the solution washed with dilute sodium hydroxide and finally distilled. 2-Hydroxy-2 : 4 : 4-trimethylpentylamine (XXV; R = H) (3 g., 43%), b. p. 83—87°/14 mm., n_D^{20} 1·4598, was obtained therefrom, and was identified as the hydrochloride, m. p. and mixed m. p. 183° (cf. above).

The chlorohydrin (XII) (10 g.) was distilled from anhydrous oxalic acid (10 g.). Some water first distilled, followed by an oil, which was taken up in ether, washed, dried, and fractionated giving a *trimethylchloropentene*, b. p. 151—152°, n_D^{20} 1·4438—1·4445 (Found : C, 65·2; H, 10·8; Cl, 23·7; active H, nil. $C_8H_{15}Cl$ requires C, 65·5; H, 10·3; Cl, 24·2%) (chlorodi*iso*butylene has b. p. 53—54°/20 mm., n_D^{20} 1·4473; Umnowa, *loc. cit.*).

The chlorohydrin (XII) (5 g.), potassium permanganate (5 g.), sodium hydroxide (3 g.), and water (100 ml.) were heated on a steam-bath with occasional shaking for 4—5 hr. Manganese dioxide and a small oily layer were removed, and the aqueous solution was acidified and extracted with ether, giving α-hydroxy-αγγ-trimethylvaleric acid (VI), m. p. 107° not depressed by the material obtained as above.

With sodium sulphite. Epoxide (I) (64 g., 0·5 mole), sodium sulphite heptahydrate (126 g., 0·5 mole), and water (500 ml.) were stirred in a stainless-steel autoclave at 140—150° for 6 hr. An oily layer was separated from the product with ether, and the aqueous solution soon deposited a white crystalline solid. This was filtered off and washed with ice-cold water and then ethanol; further crops were obtained on concentration of the mother-liquor, giving a total

of 74·5 g. (55%). After recrystallisation from 95% ethanol, sodium 2-hydroxy-2 : 4 : 4-trimethylpentane-1-sulphonate (XIII) formed colourless lustrous plates of the *monohydrate*, m. p. 202° [Found : C, 38·6; H, 7·6; S, 12·7; ash, 28·6; loss in vacuum at 100°, 7·3. $C_8H_{17}O_4SNa,H_2O$ requires C, 38·4; H, 7·7; S, 12·8; ash (Na_2SO_4), 28·4; H_2O, 7·2%]. The S-*benzylthiuronium salt* crystallised from aqueous ethanol in laths, m. p. 135° (Found : C, 51·1; H, 7·3. $C_8H_{10}N_2S,C_8H_{18}O_4S$ requires C, 51·1; H, 7·5%). Distillation of the oily product afforded mainly 4 : 4-dimethylpentan-2-one, b. p. 115—125°/760 mm. (identified as dinitrophenylhydrazone), and the diol (II), m. p. 60—62°.

The hydroxy-sulphonate (XIII) (25 g.) and acetic anhydride (75 ml.) were refluxed gently for 15 min., water was added, and the bulk of the acetic acid removed by steam-distillation. A solid crystallised on cooling, which was recrystallised from 90% ethanol giving an unsaturated *sulphonate monohydrate* as plates, m. p. 216° (decomp.) (Found : C, 41·8; H, 7·5; S, 13·3. $C_8H_{15}O_3SNa,H_2O$ requires C, 41·4; H, 7·4; S, 13·8%). The S-*benzylthiuronium salt*, m. p. 153—157°, was prepared in aqueous solution. On repeated recrystallisation from ethanol the least soluble fraction formed needles, m. p. 180—181° (Found : C, 53·9; H, 7·4. $C_8H_{10}N_2S,C_8H_{16}O_3S$ requires C, 53·6; H, 7·3%). No pure component could be isolated from the mother-liquors.

An aqueous solution of the unsaturated sulphonate (6 g.) was hydrogenated over Adams's catalyst. Hydrogen equivalent to 0·8 double bond per mole was absorbed. The filtered solution was evaporated to dryness and the residual solid (5 g.) triturated with ethanol and recrystallised from 90% ethanol; *sodium* 2 : 4 : 4-*trimethylpentane*-1-*sulphonate* (XIV) *monohydrate* formed plates of indefinite m. p. (Found : C, 40·6; H, 8·1. $C_8H_{17}O_3SNa,H_2O$ requires C, 41·0; H, 8·2%). The S-*benzylthiuronium salt* crystallised from aqueous ethanol in long blunt-ended needles, m. p. 151° (Found : C, 53·4; H, 7·9; N, 7·6. $C_8H_{10}N_2S,C_8H_{18}O_3S$ requires C, 53·3; H, 7·8; N, 7·8%).

With potassium cyanide. Epoxide (I) (128 g., 1 mole), 96% potassium cyanide (68 g., 1 mole), potassium hydroxide (2 or 3 pellets), and water (400 ml.) were heated in an autoclave at 130—140° for 5 hr. The product had a strong ammoniacal odour. The oily layer was isolated in ether and fractionated. 4 : 4-Dimethylpentan-2-one and unchanged epoxide (25% of the charge) came over first, followed by fractions (i) b. p. 85—110°/14 mm., (ii) 110—125°/14 mm., (iii) 125—140°/14 mm., and (iv) 150—170°/14 mm. Fraction (ii) was mainly the 1 : 2-diol (II) (4%), m. p. 60°. Fraction (iv) was identified as the dihydroxy-amine (XXVI; R = H) (20%), by preparation of the sulphate, m. p. 222°, and picrate, m. p. 149°, neither depressed by authentic samples. Fraction (i) was redistilled, and gave a main product, b. p. 85—86°/12 mm., n_D^{20} 1·4528, which appeared to be substantially 2 : 4 : 4-*trimethylpent*-1-*enyl cyanide* (XXXVII) (9%) (Found : C, 78·8; H, 11·6; N, 10·2. $C_9H_{15}N$ requires C, 78·8; H, 11·0; N, 10·2%). The infra-red absorption spectrum had bands at 819 and 835 $cm.^{-1}$, characteristic of trisubstituted ethylenes, thus confirming the vinyl cyanide structure. Fraction (iii) was redistilled and gave a fraction, b. p. 125—132°/14 mm. (14%), n_D^{20} 1·4525—1·4529, of a basic substance [Found : C, 74·3; H, 13·0; active H, 0·47%; equiv., 251. $C_{16}H_{32}ON(H)$ requires C, 75·2; H, 13·0; active H, 0·3%; equiv., 255].

Miscellaneous Reactions.—With sodium alkyl or aralkyl sulphides. (*a*) Methanethiol (from 55·5 g. = 0·40 mole of methylthiuronium sulphate; cf. *Org. Synth.*, Coll. Vol. II, p. 345) was passed into ethanol (150 ml.) containing sodium ethoxide (from sodium, 8 g., 0·34 mole). The epoxide (I) (50 g., 0·39 mole) was then added slowly; an exothermic reaction took place, the temperature rising to 40°. The mixture was finally warmed to 70°, and next morning was diluted with water. The oily product was isolated in ether, well washed, dried, and distilled. The fraction of b. p. 90—98°/14 mm. (23·6 g., 38% on sodium used) was redistilled, giving 2 : 4 : 4-*trimethyl*-1-*methylthiopentan*-2-*ol* (XV; R = Me), b. p. 96—98°/14 mm., n_D^{20} 1·4749 [Found : C, 62·0; H, 11·6; S, 17·5; active H, 0·6. $C_9H_{19}S(OH)$ requires C, 61·3; H, 11·5; S, 18·2; active H, 0·57%].

A mixture of this product (7 g.), Raney nickel (100 g.), and ethanol (50 ml.) was refluxed for 5 hr. The filtrate and ethanol washings from the nickel were distilled, first removing ethanol and then the whole of the remaining liquid product, and leaving a whitish inorganic residue. The product was taken up in ether, traces of ethanol were washed out with water, and when dried it was redistilled. A main fraction, n_D^{20} 1·4238, was collected at 143—145° (Found : C, 73·3; H, 14·0. Calc. for $C_8H_{18}O$: C, 73·8; H, 13·9%). This was shown to contain at least 90% of 2 : 4 : 4-trimethylpentan-2-ol (XVI), by comparison of its infra-red absorption spectrum with that of an authentic sample, b. p. 145—146°, n_D^{20} 1·4281, prepared by Ritter's method (*loc. cit.*) (Found : C, 73·5; H, 14·0%).

(*b*) Toluene-ω-thiol (12·4 g., 0·1 mole), sodium hydroxide (6 g., 0·15 mole), water (10 ml.), ethanol, and (I) (14·0 g., 0·109 mole) were refluxed for 2·5 hr. The oil which separated on pouring of the product into water was taken up in ether, washed with dilute sodium hydroxide, then water, dried, and distilled. The fraction, b. p. 175—185°/14 mm. (19·0 g., 75%), was redistilled, giving **1-*benzylthio*-2 : 4 : 4-*trimethylpentan*-2-*ol*** (XV; R = CH_2Ph), b. p. 104—105°/0·1 mm., n_D^{20} 1·5290 (Found: C, 71·5; H, 9·5. $C_{15}H_{24}OS$ requires C, 71·4; H, 9·5%).

With methylmagnesium iodide. The epoxide (I) (64 g., 0·5 mole) reacted gently with methylmagnesium iodide (0·5 mole) in ether. After hydrolysis with 2N-hydrochloric acid, the product on distillation gave a badly coloured main fraction (22·5 g., 31%), b. p. 73—76°/15 mm., and a large resinous residue. Redistillation of the main fraction gave fractions, still badly coloured: (i) b. p. 71·5—72°/14 mm. (7·2 g.), n_D^{20} 1·4382, (ii) 72—73·5°/14 mm. (7·6 g.), n_D^{20} 1·4390, (iii) 73·5—77°/14 mm. (6·0 g.), n_D^{20} 1·4420. Comparison of the infra-red spectra of fractions (i) and (iii) with that of synthetic **3 : 5 : 5-trimethylhexan-2-ol** (XX) (see below) indicated that each contained approximately 50% of this alcohol, and that the other component of the mixture gave a strong hydroxyl band and an ethyl band. This second component is therefore probably **3 : 5 : 5-trimethylhexan-3-ol**. Fraction (ii) gave a **3 : 5-dinitrobenzoate**, m. p. 39—40° not raised by further recrystallisation.

2 : 4 : 4-Trimethylpentanal (XXIV) and methylmagnesium iodide (0·5 mole of each) were allowed to react in ether, affording after the usual procedure **3 : 5 : 5-trimethylhexan-2-ol** (XX) as a pale yellow liquid, b. p. 75—80°/18 mm., n_D^{20} 1·4325 (71%), giving a **3 : 5-*dinitrobenzoate***, m. p. 61° (Found: C, 56·9; H, 6·5. $C_{16}H_{22}O_6N_2$ requires C, 56·8; H, 6·6%).

With ethyl acetoacetate. Sodium (11·5 g., 0·5 mole) was "powdered" under toluene and transferred to dry dioxan. Ethyl acetoacetate (65 g., 0·5 mole) was added slowly, dissolution of the sodium being finally hastened by warming. This solution together with epoxide (I) (64 g., 0·5 mole) was heated in an autoclave for 5 hr. at 150°. Water was added to the product followed by dilute sulphuric acid until acid, and the oily product was extracted with ether, washed, dried, and fractionated. A main fraction, b. p. 104—115°/0·7 mm. (21·1 g.), n_D^{20} 1·4614, was collected, together with low- and high-boiling by-products. From its analysis this product was a mixture, but it readily gave a pale yellow **2 : 4-*dinitrophenylhydrazone***, m. p. 114—115°, from aqueous ethanol and then methanol, of composition approximately that of the derivative of (XVIII) (Found: C, 55·6; H, 5·7; N, 13·4. $C_{20}H_{30}O_7N_4$ requires C, 55·2; H, 6·2; N, 14·3%).

The product (10 g.) was hydrolysed by boiling it with potassium hydroxide (4 g.) in water (100 ml.) and ethanol (50 ml.) for 4 hr. The organic layer was worked up to yield a fraction, b. p. 105—115°/12 mm. (mostly 112°/12 mm.; 2·7 g.), n_D^{20} 1·4430. This gave an equivalent weight by hydroxylamine titration of 238 [calc. for hydroxy-ketone (XIX), 188], so the product was probably a mixture. It did, however, give a yellow **2 : 4-*dinitrophenylhydrazone***, m. p. 81—82° (from ethanol), which gave analyses in approximate agreement with the derivative of 2-methyl-4-oxo-2-*neo*pentylpentan-1-ol (XIX) (Found: C, 55·5; H, 6·9; N, 15·4. $C_{17}H_{26}O_5N_4$ requires C, 56·1; H, 7·2; N, 15·4%).

Hydrogenation. (*a*) The epoxide (I) (256 g.; b. p. 138—142°) was hydrogenated in an autoclave, Raney nickel (in the minimum quantity of ethanol) being used as catalyst. The hydrogen pressure was raised initially to 100 atm. Absorption started when the temperature reached 100°, with slight evolution of heat, and was complete in 2—3 hr. at 110—120°. The decrease in pressure corresponded to an absorption of 110% of the theoretical amount of hydrogen. The catalyst was found to be coagulated with separated water. The product was fractionated, and **2 : 4 : 4-trimethylpentan-1-ol** (XXI) (128 g., 50%), b. p. 73—77°/16 mm., was obtained. The lower-boiling material consisted of water, **2 : 4 : 4-trimethyl-pentane** and **-pent-1-ene** (identified by infra-red examination), and a little unchanged epoxide.

(*b*) 291 g. of epoxide were similarly hydrogenated, but with addition of 50 ml. of dioxan and 2 drops of 40% sodium hydroxide solution. The reaction was finished in 4 hr. at 110—120°. The product was similar in composition to that obtained in (*a*), but the yield of trimethylpentanol was 60%.

(*c*) Hydrogenation of epoxide (I) in the vapour phase over 5% nickel–pumice at 200° yielded trimethylpentanol, some unchanged epoxide, water, and hydrocarbon (trimethylpentene containing a little trimethylpentane). The yield of trimethylpentanol was 40—50%.

We are indebted to Mr. H. C. Highet for the vapour-pressure data, to Mr. A. R. Philpotts for the spectroscopic work and its interpretation, and to Mr. W. S. Wise for measuring

dissociation constants. We thank Mr. F. E. Salt and Dr. K. H. W. Turck for their interest in the work described in this series of papers, and the Directors of the Distillers Company Ltd. for permission to publish the results.

THE DISTILLERS COMPANY LIMITED, RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM, SURREY. [*Received, December 29th*, 1953.]

Organic Peroxides. Part III. The Preparation of Alkyl Hydroperoxides and Dialkyl Peroxides. Characteristic Derivatives of Alkyl Hydroperoxides.*

By A. G. DAVIES, R. V. FOSTER, and A. M. WHITE.

[Reprint Order No. 5102.]

The preparation of alkyl hydroperoxides by the reaction between 90% hydrogen peroxide and the carbonium ions obtained by the unimolecular alkyl–oxygen heterolysis of alcohols or carboxylic esters, or by the protonation of olefins (Part I *), has been extended to several new alkyl hydroperoxides. In analogous preparations of dialkyl peroxides, carbonium ions react with an alkyl hydroperoxide; the alkylation of alkyl hydroperoxides with xanthhydrol or triphenylmethanol produces crystalline derivatives suitable for the characterisation of the hydroperoxides.

Preparation of Alkyl Hydroperoxides.—We have shown (*Nature*, 1952, **170**, 668; *J.*, 1952, 3300; Part I,* and unpublished work on isotopically labelled compounds) that alkyl hydroperoxides may be prepared by nucleophilic attack of concentrated hydrogen peroxide on carbonium ions ($R^+ + HO{\cdot}OH \longrightarrow RO{\cdot}OH + H^+$) which may be generated by the unimolecular alkyl–oxygen heterolysis of alcohols or of carboxylic esters, or by the protonation of olefins. These reactions have now been extended to the preparation of a number of new alkyl hydroperoxides.

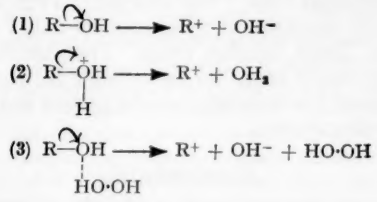
Good yields of 1-ethyl-1-methylbutyl, 4-methoxydiphenylmethyl, 4-phenyldiphenylmethyl, 1-methyl-1-phenylpropyl, and xanthhydryl hydroperoxide were obtained from the corresponding alcohols and 90% hydrogen peroxide. The conclusions reached in Part I * have been confirmed in that the reactivity of the various alcohols, as determined by the weakest acid which will bring about the reaction, is again parallel to their known tendency to undergo unimolecular alkyl–oxygen heterolysis (Kenyon and his co-workers, *J.*, 1942—54). Thus in the extremes, xanthhydrol, which is very reactive by such a mechanism (Balfe, Kenyon, and Thain, *J.*, 1952, 790), reacts with 90% hydrogen peroxide in homogeneous ethereal solution, and even with neutral 30% aqueous hydrogen peroxide, whereas benzyl alcohol was recovered after treatment with 90% hydrogen peroxide and concentrated sulphuric acid.

1-Methyl-1-phenylpropyl hydroperoxide has also been obtained by the solvolysis of 1-methyl-1-phenylpropyl hydrogen phthalate in 90% hydrogen peroxide containing an excess of sodium hydrogen carbonate, and 1-ethyl-1-methylbutyl hydroperoxide by the addition of hydrogen peroxide to the olefin derived from 3-methylhexan-3-ol (probably a mixture of 3-methylhex-2- and -3-ene).

Factors influencing Alkyl–Oxygen Heterolysis of Alcohols in Hydrogen Peroxide.—The high reactivity of certain alcohols towards hydrogen peroxide is noteworthy, and has been further investigated. Whereas 1 : 2 : 3 : 4-tetrahydro-1-naphthol (Part I) and xanthhydrol react readily with 90% hydrogen peroxide in the absence of added acid, this reactivity is completely suppressed by the addition of sodium hydrogen carbonate to the solution. Xanthhydrol reacts even with neutral 30% hydrogen peroxide, but 1 : 2 : 3 : 4-tetrahydro-1-naphthol reacts with this reagent only in the presence of sulphuric acid.

* Part I and II, *J.*, 1953, 1541, 1808.

To account for this unimolecular alkyl–oxygen heterolysis of alcohols in ostensibly neutral hydrogen peroxide, the following mechanisms may be considered :



The first, involving alkyl–oxygen heterolysis in the absence of catalysis (except for the usual solvation) is rather improbable in view of the strong nucleophilic power of the HO^- anion for a carbonium ion, and no previous examples appear to have been reported.

The assumption implicit in the second mechanism, that hydrogen peroxide is of itself * an acid strong enough to protonate the basic OH group in 1 : 2 : 3 : 4-tetrahydro-1-naphthol or xanthhydrol, and thus catalyse alkyl–oxygen heterolysis may well be true of 90% hydrogen peroxide, but seems less likely for dilute aqueous hydrogen peroxide. Mitchell and Wynne-Jones have shown (*Discuss. Faraday Soc.*, 1953, **15**, 161) that the acidity of pure hydrogen peroxide is about 10^9 times greater than that of water; this acidity is emphasised by the fact that we find that 90% hydrogen peroxide reacts vigorously with sodium hydrogen carbonate with the evolution of carbon dioxide without loss of oxygen. Aqueous 50% hydrogen peroxide reacts very slowly, and 30% hydrogen peroxide is unreactive.†

The weakening of the alkyl–oxygen bond by the formation of a hydrogen bond between an H_2O_2 molecule and the oxygen atom of the alcoholic group (eqn. 3) would be analogous to that postulated (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1266) for the replacement of OH by halogen with halogen hydracids. In view of the known ability of hydrogen peroxide to form strong hydrogen bonds (Scatchard, Kavanagh, and Ticknor, *J. Amer. Chem. Soc.*, 1952, **74**, 3715) this seems the most probable cause of the reactivity of xanthhydrol towards neutral 30% hydrogen peroxide.

Preparation of Dialkyl Peroxides.—By analogy with our methods of preparation of alkyl hydroperoxides, reactions in which carbonium ions are generated in media containing alkyl hydroperoxides might be expected to yield dialkyl peroxides ($R^+ + R'O{\cdot}OH \longrightarrow RO{\cdot}OR' + H^+$). This has been confirmed, and examples of such reactions have been established in which the carbonium ion is again produced by alkyl–oxygen heterolysis of alcohols and of esters, or by protonation of olefins.

Xanthhydrol and triphenylmethanol in acetic and acetic–sulphuric acid solution, respectively, react readily with alkyl hydroperoxides to form the corresponding crystalline alkyl xanthhydryl or alkyl triphenylmethyl peroxides in good yields (see Table). Attempts to prepare di-*p*-methoxyphenylmethyl hydroperoxide from the alcohol and hydrogen peroxide gave only bis(di-*p*-methoxyphenylmethyl) peroxide. Apparently the alkyl hydroperoxide which is first formed is then alkylated by a second molecule of the alcohol which very readily undergoes alkyl–oxygen heterolysis (Balfe, Kenyon, and Thain, *J.*, 1951, 386; 1952, 790).

1-Methyl-1-phenylpropyl hydrogen phthalate in acetic–sulphuric acid readily reacts with *tert.*-butyl hydroperoxide, to form *tert.*-butyl 1-methyl-1-phenylpropyl peroxide, identical with the product of the analogous reaction of 2-phenylbutan-2-ol. The reaction of alkyl hydroperoxides with olefins has been exemplified by the preparation of *tert.*-amyl *tert.*-butyl peroxide from 2-methylbut-2-ene and *tert.*-butyl hydroperoxide, under similar acid conditions.

Various crystalline esters are available for the characterisation of saturated *tert.*-alkyl hydroperoxides; Criegee and Dietrich (*Annalen*, 1948, **560**, 135) have prepared the *p*-nitro-

* The hydrogen peroxide used contained no acidic stabiliser.

† The medium for the solvolysis of hydrogen phthalic esters, which we have described (Part I) as 90% hydrogen peroxide containing sodium hydrogen carbonate, thus in fact contains very few hydrogen carbonate anions.

perbenzoates, and we have described the 1-hydrogen 1-monoperphthalates (Part I) and the percarbamates (Part II). None of these derivatives, however, can readily be prepared from the 1-arylalkyl hydroperoxides. For example, 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide with phthalic anhydride in pyridine gives only 1 : 2 : 3 : 4-tetrahydro-1-oxonaphthalene (A. M. White, Thesis, London, 1953). The xanthhydryl and triphenylmethyl derivatives described here should therefore be valuable for the isolation and characterisation of the hydroperoxides of low molecular weight present in the products of the autoxidation or combustion of hydrocarbons.

Experimental

Light petroleum refers to the fraction with b. p. 40—60°. Unless otherwise stated, solutions in organic solvents were dried over anhydrous sodium sulphate. Unstabilised 85—90% hydrogen peroxide and 60% *tert.*-butyl hydroperoxide were supplied by Messrs. Laporte Chemicals Ltd., Luton.

Explosion Hazards.—In all reactions involving organic peroxides, precautions were taken to minimise the effect of a possible explosion. No such explosion was encountered, and none of the peroxides described appears to be liable to explode in presence of traces of acid or dust, or on scratching, at temperatures below about 100°. It is recommended, however, that the reactions should not be carried out on a large scale until detonation tests on the reaction mixtures and products have indicated more clearly the hazards involved.

Purification of Commercial 60% tert.-*Butyl Hydroperoxide.*—The commercial material contains some free hydrogen peroxide which is best removed before distillation is attempted. The 60% *tert.*-butyl hydroperoxide is diluted with an equal volume of light petroleum, washed three times with water, and then thoroughly dried. Distillation from a bath at 65° gives a first fraction (b. p. 35—45°/85 mm.) consisting mainly of *tert.*-butyl peroxide, after which the *tert.*-butyl hydroperoxide distills, b. p. 36°/16 mm. The yield is about 40%.

Reaction between 85—90% *Hydrogen Peroxide and Alcohols.*—(i) 3-*Methylhexan*-3-*ol.* A mixture of the alcohol (3·4 g.; b. p. 52—54°/20 mm.), 90% hydrogen peroxide (5 c.c.), and concentrated sulphuric acid (0·04 c.c.) was stirred for 6 hr. at room temperature; water was then added, the solution extracted with ether, and the ethereal extract washed and dried. Two distillations yielded 1-*ethyl*-1-*methylbutyl hydroperoxide* (3·0 g.), b. p. 34°/0·1 mm., n_D^{20} 1·4300 (Found: C, 63·7; H, 12·0. $C_7H_{16}O_2$ requires C, 63·7; H, 12·2%). By the method described in Part I (*loc. cit.*), from the hydroperoxide (0·5 g.), phthalic anhydride (0·6 g.), and pyridine (0·45 g.), after 2 days at room temperature, 1-(1-*ethyl*-1-*methylbutyl*) *hydrogen* 1-*monoperphthalate* (0·82 g.) was obtained which, recrystallised from ether–light petroleum, showed m. p. 90—92° (Found: C, 63·8; H, 7·0%; equiv., 279. $C_{15}H_{20}O_5$ requires C, 64·2; H, 7·2%; equiv., 280).

(ii) 4-*Methoxydiphenylmethanol.* The alcohol (2·0 g.) in ether (10 c.c.) was stirred for 6 hr. with 90% hydrogen peroxide (10 c.c.) and 98% formic acid (0·02 c.c.). An ethereal extract of the diluted mixture yielded 4-*methoxydiphenylmethyl hydroperoxide* as white needles (from light petroleum), m. p. 50—51° (Found: C, 72·4; H, 6·6. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1%). From a similar reaction with concentrated sulphuric acid as the catalyst, only the products of acid decomposition, *p*-methoxyphenol (0·9 g., m. p. and mixed m. p. 52·5—53°) and benzoic acid (0·04 g.; m. p. and mixed m. p. 120·5°) were isolated.

(iii) 4-*Phenyldiphenylmethanol.* After 6 hours' stirring, a mixture of the alcohol (1·0 g.) in ether (10 c.c.), hydrogen peroxide (10 c.c.), and concentrated sulphuric acid (0·02 c.c.) was diluted with water, and extracted with ether, yielding a solid (1·0 g.) which was recrystallised from benzene, giving 4-*phenyldiphenylmethyl hydroperoxide* as leaflets, m. p. 162·5—163° (Found: C, 83·4; H, 6·0. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

(iv) 2-*Phenylbutan*-2-*ol.* The alcohol (5·0 c.c.), 90% hydrogen peroxide (5 c.c.), and concentrated sulphuric acid (0·05 c.c.) were stirred at room temperature for 6 hr. Water (10 c.c.) was then added, and the upper organic layer extracted with light petroleum, washed with water, and dried. Distillation yielded 1-methyl-1-phenylpropyl hydroperoxide, b. p. 60°/0·01 mm., n_D^{20} 1·5230.

(v) *Xanthhydrol.* The alcohol (2·0 g.) in ether (10 c.c.) was stirred for 4 hr. with 90% hydrogen peroxide (10 c.c.). *Xanthhydryl hydroperoxide* (1·77 g.) was precipitated by the addition of light petroleum to the ethereal extract of the diluted mixture, and recrystallised from ether–light petroleum mixture as colourless prisms, m. p. 123—124° (Found: C, 73·0; H, 4·6. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·6%). The same product was obtained with aqueous 30% hydrogen peroxide, and with a homogeneous solution of 90% hydrogen peroxide (5 c.c.) in ether (about 30 c.c.).

(vi) *Di*-p-*methoxyphenylmethanol*. After 4 hours' stirring, the alcohol (1·0 g.) in ether (10 c.c.), hydrogen peroxide (10 c.c.), and 98% formic acid (0·02 c.c.) yielded *bis*(*di*-p-*methoxyphenylmethyl*) *peroxide* (0·60 g.) as white needles (from ether–light petroleum mixture), m. p. 128·5—129·5° (Found: C, 74·5; H, 6·3. $C_{30}H_{30}O_6$ requires C, 74·1; H, 6·2%).

Benzyl alcohol was recovered unchanged from reaction mixtures containing sulphuric acid or formic acid as catalysts. 4-Methyldiphenylmethanol reacted in the presence of sulphuric acid, but not formic acid; the hydroperoxide was an unstable oil, which did not solidify.

Reaction between 85—90% *Hydrogen Peroxide and* 1-*Methyl*-1-*phenylpropyl Hydrogen Phthalate*.—From an initially homogeneous solution of the hydrogen phthalate (2·0 g., 1·0 mol.) in hydrogen peroxide (10 c.c.) containing sodium hydrogen carbonate (1·5 g., 2·6 mols.) at 0°, an oil separated on the surface after 2 hr. After a further 20 hr., water (25 c.c.) was added; a light petroleum extract yielded an oil (0·59 g.) which on distillation gave 1-methyl-1-phenylpropyl hydroperoxide, b. p. 72—73°/0·02 mm., n_D^{20} 1·5224 (Found: C, 72·3; H, 8·8. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·4%); Ivanov, Savinova, and Zhakhovskaya (*Doklady Acad. Nauk S.S.S.R.*, 1948, **59**, 905) report b. p. 48—49°/0·002 mm., n_D^{20} 1·5208, and Hawkins (*J.*, 1949, 2076) reports b. p. 58—58·5°/0·01 mm., n_D^{20} 1·5206.

Reaction between 85—90% *Hydrogen Peroxide and* 3-*Methylhexenes*.—The olefin, b. p. 84—96°, probably a mixture of 3-methylhex-3- and -2-ene, was obtained by heating 3-methylhexan-3-ol under reflux with 1% of iodine (Edgar, Calingaert, and Marker, *J. Amer. Chem. Soc.*, 1929, **51**, 1486). This olefin (5 c.c., 3·7 g.) was stirred with hydrogen peroxide (5 c.c.) and concentrated sulphuric acid (0·02 c.c.) in a sealed flask to prevent evaporation of the olefin. After 6 hr., water was added (25 c.c.). The ethereal extract yielded the crude hydroperoxide (2·6 g.) which was distilled, giving 1-ethyl-1-methylbutyl hydroperoxide (1·4 g.), b. p. 36—37°/0·2 mm., n_D^{20} 1·4304. From this, the hydrogen perphthalate was prepared, having m. p. and mixed m. p. 90—92°.

Reaction between Alkyl Hydroperoxides and Alcohols.—The alkyl hydroperoxides used were analysed specimens prepared as described above, or as in Part I (*loc. cit.*).

Second group	M. p.	Solvent	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Alkyl xanthhydryl peroxides.							
Me_3C	69—71°	Aq. EtOH	75·7	7·0	$C_{17}H_{18}O_3$	75·6	6·7
$EtMe_2C$	41—42	,,	75·7	7·0	$C_{18}H_{20}O_3$	76·1	7·0
PrEtMeC	liquid	—	—	—	—	—	—
PhMeCH	84—86	Pet, 1	79·5	5·9	$C_{21}H_{18}O_3$	79·2	5·7
Ph_2CH	117	Pet, 2	81·6	5·4	$C_{26}H_{20}O_3$	82·1	5·3
α-Tetralyl	125	$COMe_2$	79·9	6·1	$C_{23}H_{20}O_3$	80·2	5·9
$PhMe_2C$	97—98	Pet, 1	79·2	6·2	$C_{22}H_{20}O_3$	79·5	5·9
PhEtMeC	82—83	EtOH	79·6	6·4	$C_{23}H_{22}O_3$	79·8	6·4
Xanthhydryl	152—153	EtOH	79·3	4·7	$C_{26}H_{18}O_4$	79·2	4·6 [a]
Alkyl triphenylmethyl peroxides.							
Me_3C	72·5—73	MeOH	83·1	7·9	$C_{23}H_{24}O_2$	83·1	7·3 [b]
$EtMe_2C$	Liquid	—	—	—	—	—	—
PrEtMeC	50—52	Aq. EtOH	83·4	8·0	$C_{26}H_{30}O_2$	83·4	8·1
PhMeCH	85—86	EtOH	84·6	6·4	$C_{27}H_{24}O_2$	85·2	6·4
Ph_2CH	86—88	Pet, 2	86·5	5·8	$C_{32}H_{26}O_2$	86·8	5·9 [c]
α-Tetralyl	91—92	EtOH	85·3	6·4	$C_{29}H_{26}O_2$	85·7	6·4 [d]
$PhMe_2C$	168—169	[e]	85·3	5·9	$C_{28}H_{26}O_2$	85·3	6·6

Pet = light petroleum, 1 = b. p. 40—60°, 2 = b. p. 100—120°.

[a] Xanthhydryl peroxide may also be obtained by warming xanthhydryl hydroperoxide in acetic acid (see succeeding paper). [b] Kharasch *et al.*, *J. Org. Chem.*, 1951, **16**, 1465, report m. p. 72—73°. [c] Bachman and Wiselogle, *ibid.*, 1937, **1**, 354, report m. p. 93—94° for this compound obtained by the autoxidation of pentaphenylethane. [d] Kharasch and Burt, *ibid.*, 1951, **16**, 150, report m. p. 96—97°. [e] The solid, precipitated from solution during the reaction, was insoluble in common organic solvents, and was purified by washing with a large volume of hot ethanol.

(i) *Reaction between* 2-*phenylbutan*-2-*ol and* tert.-*butyl hydroperoxide*. A solution of the alcohol (7·5 g.) and *tert.*-butyl hydroperoxide (4·5 g.) in glacial acetic acid (15 c.c.) containing concentrated sulphuric acid (0·5 g.) became opalescent after 0·5 hr. and a lower liquid layer separated. After 5 hours' stirring, water (45 c.c.) was added, and the product extracted with ether, washed with saturated aqueous potassium carbonate till neutral, and dried (K_2CO_3). Distillation yielded tert.-*butyl* 1-*methyl*-1-*phenylpropyl peroxide* (7·17 g.), b. p. 50—51°/0·4 mm., n_D^{25} 1·4786, d_4^{25} 0·932 (Found: C, 76·0; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

(ii) *Preparation of xanthhydryl derivatives of alkyl hydroperoxides*. The alkyl hydroperoxide

(0·5 g.), dissolved in chloroform if a solid, was added to a solution of xanthhydrol (1 mol.) in glacial acetic acid (10 c.c.). After 0·5—1 hr. at room temperature (with stirring if solid had separated), the mixture was poured on crushed ice, and the precipitated *alkyl xanthhydryl peroxide* was recrystallised. Yields of recrystallised material were usually better than 60%. Details of solvents, m. p., and analyses are given in the Table.

(iii) *Preparation of triphenylmethyl derivatives of alkyl hydroperoxides.* The alkyl hydroperoxide (0·5 g.), dissolved in chloroform if a solid, was added to a solution of triphenylmethanol (1 mol.) in glacial acetic acid (20 c.c.) containing concentrated sulphuric acid (0·05 c.c.). After 2 hr. at room temperature, the mixture was poured on ice, and the *alkyl triphenylmethyl peroxide* which separated was recrystallised. Yields again were usually better than 60%. Details are given in the Table.

Reaction between tert.*-Butyl Hydroperoxide and 2-Methylbut-2-ene.*—Concentrated sulphuric acid (1·0 c.c.) was added slowly to a solution of 2-methylbut-2-ene (4·0 g.) and *tert.*-butyl hydroperoxide (5·0 g.) in acetic acid (30 c.c.), cooled in water. After 18 hr. at room temperature, the mixture was poured into water; the organic layer was washed with dilute sodium hydroxide solution and with saturated aqueous potassium carbonate and dried (K_2CO_3), yielding *tert.*-amyl *tert.*-butyl peroxide (6·0 g.), b. p. 125—127° (slight decomp.), n_D^{20} 1·3980 (Found: C, 67·3; H, 12·5. Calc. for $C_9H_{20}O_2$: C, 67·5; H, 12·5%). Rust, Dickey, and Bell (U.S.P. 2,403,758; B.P. 591,543) prepared this compound from *tert.*-butyl hydroperoxide and *tert.*-amyl alcohol, and report the b. p. of an aqueous azeotrope as 91—92°, n_D^{20} 1·4000.

Reaction between 1-Methyl-1-phenylpropyl Hydrogen Phthalate and tert.*-Butyl Hydroperoxide.*—Concentrated sulphuric acid (0·1 c.c.) in acetic acid (1·0 c.c.) was added to the hydrogen phthalate (2·31 g.) and *tert.*-butyl hydroperoxide (0·7 g.) in glacial acetic acid (20 c.c.). Scratching caused immediate precipitation of phthalic aicd (1·00 g.; m. p. 192—194°). After 10 min., the filtrate was diluted with water, and the precipitated oil extracted with ether, washed with saturated aqueous potassium carbonate till neutral, and dried (K_2CO_3). Distillation yielded *tert.*-butyl 1-methyl-1-phenylpropyl peroxide (0·55 g.), n_D^{25} 1·4786 (Found: C, 75·9; H, 9·9. Calc. for $C_{14}H_{22}O_2$: C, 75·6; H, 10·0%).

Grateful acknowledgment is made to the Governing Body of Battersea Polytechnic for the award of an Edwin Tate and Holl Scholarship to one of the authors (A. M. W.), to the Chemical Society for a grant, and to Messrs. Laporte Chemicals Ltd., Luton, for the gift of hydrogen peroxide and *tert.*-butyl hydroperoxide.

Chemistry Department, Battersea Polytechnic, London, S.W.11.
William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, February 8th*, 1954.]

Organic Peroxides. Part IV. Alkyl–Oxygen Heterolysis in Organic Peroxides.*

By A. G. Davies, R. V. Foster, and R. Nery.

[Reprint Order No. 5103.]

Alkyl hydroperoxides and dialkyl peroxides undergo unimolecular alkyl–oxygen heterolysis to form carbonium ions, which are detected by their characteristic reactions with suitable nucleophilic reagents.

Much of the interest in organic peroxides arises from the multiplicity of types of bond fission which such molecules undergo. Apart from the familiar oxygen–oxygen homolysis (Leffler, *Chem. Reviews*, 1949, **45**, 385) and the oxygen–hydrogen homolysis more recently reported (Campbell and Coppinger, *J. Amer. Chem. Soc.*, 1952, **74**, 1469; Kharasch, Pauson, and Nudenberg, *J. Org. Chem.*, 1953, **18**, 322), two types of bond heterolysis are well established. Hydrogen–oxygen heterolysis ($RO{\cdot}\overset{\curvearrowleft}{O}\!-\!H$) in alkyl hydroperoxides occurs in their nucleophilic reactions, *e.g.*, formation of dialkyl peroxides by alkylation

* Part III, preceding paper.

with alcohols and olefins (Part III *), esterification (Parts I and II, *J.*, 1953, **1541**, 1808), carbonyl addition (Rieche, *Ber.*, 1930, **63**, 2642), and epoxide addition (Barusch and Payne, *J. Amer. Chem. Soc.*, 1953, **75**, 1987). Of more recent recognition is the oxygen–oxygen heterolysis of peroxides ($RO\overset{\curvearrowright}{-}O{\cdot}R'$; Leffler, *loc. cit.*) which has been described in the reactions of peracids (Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692), in the decomposition of peresters (Criegee, *Annalen*, 1948, **560**, 127), in the acid-catalysed (Kharasch, Fono, and Nudenberg, *J. Org. Chem.*, 1950, **15**, 748) and base-catalysed (Kornblum and de la Mare, *J. Amer. Chem. Soc.*, 1951, **73**, 880) decomposition of alkyl hydroperoxides and dialkyl peroxides, and in the acid-catalysed rearrangements of diacyl peroxides (Leffler, *ibid.*, 1950, **72**, 67). This heterolysis is usually accompanied, in the RO group, by loss of a proton from the α-position, or by migration of an α-alkyl or α-aryl group on to the oxygen atom, to form ultimately a carbonyl compound or its derivative (Kharasch, Fono, Nudenberg, and Poshkus, *J. Org. Chem.*, 1950, **15**, 775).

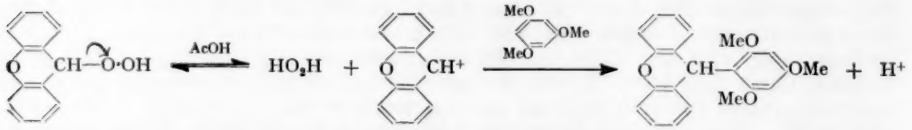
A third possible mode of bond heterolysis in alkyl hydroperoxides and dialkyl peroxides, that of alkyl–oxygen heterolysis probably by a unimolecular mechanism, *i.e.*, $RO{\cdot}OR' \overset{H^+}{\rightleftharpoons} R\overset{\curvearrowright}{-}\overset{+}{O}(H){\cdot}OR' \rightleftharpoons R'O{\cdot}OH + R^+ \xrightarrow{Y} RY$, is now described.

The affinity of an oxygen atom for the electrons of either the alkyl–oxygen or the oxygen–oxygen bond will normally be small, but bond heterolysis in both of these senses will be susceptible to acid catalysis by the increase of the electron affinity of the oxygen atom by protonation. If the electron-releasing power of the group R is small, oxygen–oxygen heterolysis usually occurs, as described above. However, if group R strongly releases electrons, then unimolecular alkyl–oxygen heterolysis may occur with comparable or greater readiness, leading to the formation of carbonium ions; thus it is in compounds such as the xanthhydryl, triphenylmethyl, and di-*p*-methoxyphenylmethyl peroxides, under acid conditions, that unimolecular alkyl–oxygen fission may be expected (Parts I and III, *locc. cit.*). The presence of the carbonium ions in solution may be detected by their characteristic reactions with suitable nucleophilic reagents, as demonstrated by Kenyon and his co-workers (*J.*, 1942—54) for alcohols and esters.

The simplest reaction of this type which we have encountered is the disproportionation reaction of xanthhydryl hydroperoxide in acetic acid solution. It occurs rapidly on warming, more slowly at room temperature, to give xanthhydryl peroxide and hydrogen peroxide. One molecule of the hydroperoxide, by undergoing unimolecular alkyl–oxygen fission (as to the reactivity of xanthhydrol by a similar mechanism, see Balfe, Kenyon, and Thain, *J.*, 1952, 790, and Part III, *loc. cit.*), provides a carbonium ion which alkylates a second alkyl hydroperoxide molecule, *i.e.*, $X\overset{\curvearrowright}{-}O{\cdot}OH \overset{H^+}{\rightleftharpoons} HO{\cdot}OH + X^+ \xrightarrow{XO{\cdot}OH} XO{\cdot}OX + H^+$ (X = xanthhydryl). This disproportionation reaction is a general characteristic of molecules which contain a nucleophilic centre and can undergo unimolecular alkyl–oxygen heterolysis (*e.g.*, alcohols, alkyl hydrogen phthalates, and alkyl hydrogen sulphates).

The presence of intermediate carbonium ions has also been demonstrated by their reactions with the following added nucleophilic reagents: (*a*) aromatic compounds reactive to electrophilic substituting agents, (*b*) sodium toluene-*p*-sulphinate, (*c*) urea, (*d*) ethyl acetoacetate, and (*e*) acetone. In all cases the experiments with the peroxide have been preceded by an experiment with the corresponding alcohol, and the identity of the products obtained by alkyl–oxygen heterolysis from the two reactions has been confirmed. For the characterisation of carbonium ions by the use of aromatic compounds we have employed 1 : 3 : 5-trimethoxy- and 1 : 3 : 5-triethoxy-benzene. These are readily alkylated by xanthhydrol or di-*p*-methoxyphenylmethanol in acetic acid, and by 1 : 2 : 3 : 4-tetrahydro-1-naphthol in acetic–sulphuric acid, to give the corresponding alkylated trialkoxybenzene in good yield. The reactions of alcohols with reagents (*b*), (*c*), and (*d*) have been described by Kenyon *et al.* (*loc. cit.*), except the preparation of 1-methyl-1-phenylpropyl *p*-tolyl sulphone, which is now reported.

Xanthhydryl hydroperoxide, xanthhydryl peroxide, bis(di-*p*-methoxyphenylmethyl) peroxide, and 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide react with the *s*-trialkoxybenzenes under the same conditions as the corresponding alcohols, to yield the respective alkylated aromatic compounds, *e.g.*:



From the reactions of the last two peroxides, some of the products of oxygen–oxygen heterolysis were also isolated.

Xanthhydryl peroxide and sodium toluene-*p*-sulphinate in acetic acid give *p*-tolyl xanthhydryl sulphone in good yield. The same product was obtained from the unsymmetrical peroxides, 1 : 2 : 3 : 4-tetrahydro-1-naphthyl xanthhydryl peroxide, and *tert.*-butyl xanthhydryl peroxide, as would be expected from the known relative tendencies of the *tert.*-butyl, 1 : 2 : 3 : 4-tetrahydro-1-naphthyl, and xanthhydryl groups to undergo unimolecular alkyl–oxygen heterolysis (Parts I and III). After reaction of *tert.*-butyl xanthhydryl peroxide, the liberated *tert.*-butyl hydroperoxide was isolated and characterised as 1-*tert.*-butyl hydrogen 1-monoperphthalate. Similarly, *tert.*-butyl triphenylmethyl peroxide, bis(di-*p*-methoxyphenylmethyl) peroxide, and *tert.*-butyl 1-methyl-1-phenylpropyl peroxide react with sodium toluene-*p*-sulphinate in acetic–sulphuric acid, to form *p*-tolyl triphenylmethyl sulphone, di-*p*-methoxyphenylmethyl *p*-tolyl sulphone, and 1-methyl-1-phenylpropyl *p*-tolyl sulphone, respectively. 1 : 2 : 3 : 4-Tetrahydro-1-naphthyl hydroperoxide and 1-methyl-1-phenylpropyl hydroperoxide do not form sulphones, but undergo the alternative reaction of reduction to the corresponding alcohols. The mechanism of the reduction is unknown, but from the fact that no sulphone could be isolated, it appears improbable that a free carbonium ion is involved at any stage in the reaction.

Again, xanthhydryl peroxide in acetic acid readily reacts with urea, and with ethyl acetoacetate, to form *s*-dixanthhydrylurea, and ethyl xanthhydrylacetoacetate, respectively, in good yield. Similarly *tert.*-butyl xanthhydryl peroxide and *tert.*-amyl xanthhydryl peroxide react with acetone under acid conditions to form xanthhydrylacetone.

The possibility merits consideration that these reactions might involve alkyl–oxygen homolysis rather than heterolysis. The following are the principal reasons why this alternative has been rejected. (*a*) All the reactions are susceptible to acid catalysis, which is interpretable on the basis of a heterolytic (see above) but hardly a homolytic mechanism. (*b*) The reaction conditions and products are always analogous to those of the corresponding alcohols. The reactivity of the latter follows the order predicted from a knowledge of the structural factors affecting the rates of S_N1 reactions (Part I); if such reactions involved free alkyl radicals it would be expected that, for example, a solution of triphenylmethanol in acetic–sulphuric acid in the presence of air would yield triphenylmethyl peroxide. (*c*) The products arising from alkyl–oxygen homolysis would probably be different from those obtained. Thus triphenylmethyl radicals do not undergo the reactions of strong electrophilic reagents; at room temperature they do not react with acetone, and form only loose molecular complexes with higher ketones, nitriles, aromatic compounds, and similar nucleophilic reagents (Gomberg, *J. Amer. Chem. Soc.*, 1914, **36**, 1144). It therefore appears safe to assume that the reactions described here proceed by alkyl–oxygen heterolysis.

Reactions of the type described above provide a method for the isolation and purification of impure alkyl hydroperoxides *via* the preparation (Part III), fractional crystallisation, and subsequent alkyl–oxygen heterolysis of their xanthhydryl or triphenylmethyl derivatives. These reactions may also provide a new route for the preparation of hydrogen peroxide by alkyl–oxygen heterolysis of alkyl hydroperoxides obtained from the autoxidation of hydrocarbons, and for the preparation of alkyl hydroperoxides by the

alkylation of a reactive alkyl hydroperoxide, followed by the removal of the reactive alkyl group by alkyl–oxygen heterolysis.

Experimental

Alkyl hydroperoxides and peroxides were prepared as described in Parts I and III (*locc. cit.*).

Reaction between Alcohols and 1 : 3 : 5-*Trimethoxy- and* 1 : 3 : 5-*Triethoxy-benzene.*—(i) *Xanthhydrol.* A mixture of xanthhydrol (1·0 g.) in glacial acetic acid (10 c.c.) and 1 : 3 : 5-trimethoxybenzene (1·0 g.) also in acetic acid (10 c.c.), after 20 hr. at room temperature, was poured over crushed ice, and the precipitate was recrystallised from butanol, yielding 1 : 3 : 5-*trimethoxy*-2-*xanthhydrylbenzene* (1·20 g.) as colourless rhombs, m. p. 159—160° (Found: C, 75·8; H, 5·7. $C_{22}H_{20}O_4$ requires C, 75·9; H, 5·8%). 1 : 3 : 5-*Triethoxy*-2-*xanthhydrylbenzene*, prepared similarly, was obtained as needles (from butanol), m. p. 157·5—158·5° (Found: C, 76·5; H, 6·8. $C_{25}H_{26}O_4$ requires C, 76·9; H, 6·7%).

(ii) *Di*-p-*methoxyphenylmethanol.* After 20 hr., a mixture of di-*p*-methoxyphenylmethanol (0·5 g.) and 1 : 3 : 5-trimethoxybenzene (0·35 g.) in acetic acid (18 c.c.) was poured over ice, yielding 2 : 4 : 6 : 4′ : 4″-*pentamethoxytriphenylmethane* (from propanol; 0·74 g.) as needles, m. p. 102—103° (Found: C, 73·2; H, 6·7. $C_{24}H_{26}O_5$ requires C, 73·1; H, 6·6%). Similarly, from the alcohol (0·5 g.) and 1 : 3 : 5-triethoxybenzene (0·43 g.), 2 : 4 : 6-*triethoxy*-4′ : 4″-*dimethoxytriphenylmethane* (0·77 g.) was obtained as needles (from propanol), m. p. 108—109° (Found: C, 73·9; H, 7·7. $C_{27}H_{32}O_5$ requires C, 74·3; H, 7·3%).

(iii) 1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthol.* A mixture of the alcohol (0·5 g.) and 1 : 3 : 5-trimethoxybenzene (0·57 g.) in acetic acid (10 c.c.) containing concentrated sulphuric acid (0·05 c.c.) after 72 hr. yielded 1 : 3 : 5-*trimethoxy*-2-(1 : 2 : 3 : 4-*tetrahydro*-1-*naphthyl*)*benzene* as irregular rhombs (0·69 g.; from light petroleum), m. p. 82—83° (Found: C, 76·3; H, 7·3. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·7%).

Reaction of 2-*Phenylbutan*-2-*ol and its Hydrogen Phthalate, with Sodium Toluene*-p-*sulphinate.*—After 72 hr., a solution of 2-phenylbutan-2-ol (0·5 g.) and sodium toluene-*p*-sulphinate (0·80 g.) in 90% formic acid (20 c.c.) was poured over crushed ice, yielding 1-*ethyl*-1-*phenylpropyl* p-*tolyl sulphone* (0·78 g.) as tablets (from aqueous methanol), m. p. 63—64° (Found: C, 71·1; H, 7·1; S, 11·1. $C_{17}H_{20}O_2S$ requires C, 70·8; H, 6·9; S, 11·1%).

Similarly, the hydrogen phthalate (0·50 g.) in acetone (3·0 c.c.) and sodium toluene-*p*-sulphinate (0·50 g.) in 90% formic acid (15 c.c.) after 72 hr. had deposited crystals of phthalic acid (0·17 g.). The supernatant solution was poured over ice, yielding the sulphone (0·25 g.; from aqueous methanol), m. p. and mixed m. p. 63—64°.

Reaction between Organic Peroxides and 1 : 3 : 5-*Trimethoxybenzene and* 1 : 3 : 5-*Triethoxybenzene.*—(i) *Xanthhydryl hydroperoxide.* Xanthhydryl hydroperoxide (0·5 g.) in chloroform (5·0 c.c.) was added to 1 : 3 : 5-trimethoxybenzene (0·40 g.) in glacial acetic acid (10 c.c.). Next day the mixture was poured over ice, yielding 1 : 3 : 5-trimethoxy-2-xanthhydrylbenzene (0·57 g.; from butanol), m. p. and mixed m. p. 159—160°. Similarly, 1 : 3 : 5-triethoxybenzene yielded 1 : 3 : 5-triethoxy-2-xanthhydrylbenzene (from butanol), m. p. and mixed m. p. 157·5—158·5°.

(ii) *Xanthhydryl peroxide.* A mixture of xanthhydryl peroxide (0·52 g.) in chloroform (5 c.c.) and 1 : 3 : 5-trimethoxybenzene (0·43 g.) in acetic acid (10 c.c.), after 72 hr. yielded 1 : 3 : 5-trimethoxy-2-xanthhydrylbenzene (from butanol; 0·79 g.), m. p. and mixed m. p. 159—160°.

(iii) *Bis*(*di*-p-*methoxyphenylmethyl*) *peroxide.* A mixture of the peroxide (0·38 g.) in chloroform (5·0 c.c.) and 1 : 3 : 5-triethoxybenzene (0·36 g.) in acetic acid (5·0 c.c.) was poured, after 14 days, over ice, and the precipitate crystallised from propanol, yielding 2 : 4 : 6-triethoxy-4′ : 4″-dimethoxytriphenylmethane (0·21 g.), m. p. and mixed m. p. 108—109°. Some red oil was also formed which was probably a decomposition product of the peroxide caused by oxygen–oxygen heterolysis.

(iv) 1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyl hydroperoxide.* The hydroperoxide (0·25 g.) in chloroform (5·0 c.c.) was added to a solution of 1 : 3 : 5-trimethoxybenzene (0·30 g.) in acetic acid (5·0 c.c.) containing concentrated sulphuric acid (0·05 c.c.). After 96 hr. the mixture was poured over ice and the oil which separated was extracted successively with light petroleum and with ether. From the light petroleum extract, 1 : 3 : 5-trimethoxy-2-(1 : 2 : 3 : 4-tetrahydro-1-naphthyl)benzene (0·05 g.) was recovered, having m. p. and mixed m. p. 81·5—82·5°. The ethereal extract yielded a dark red oil, from which an acid, probably *γ-o*-hydroxyphenylbutyric acid, was isolated, with an unsharp m. p. of 57—61°.

Reaction between Organic Peroxides and Sodium Toluene-p-*sulphinate.*—(i) *Xanthhydryl peroxide.* From a solution of xanthhydryl peroxide (0·2 g.) and sodium toluene-*p*-sulphinate (0·22 g.) in acetic acid (15 c.c.), colourless crystals began to separate after 2 hr. Recrystallisation from ethanol gave *p*-tolyl xanthhydryl sulphone (0·26 g.), m. p. and mixed m. p. 214—215° to a red liquid.

(ii) 1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyl xanthhydryl peroxide.* A suspension of the peroxide (0·42 g.) in a solution of sodium toluene-*p*-sulphinate (0·28 g.) in acetic acid (7 c.c.) was stirred for 2 hr. and then diluted with water, yielding *p*-tolyl xanthhydryl sulphone (0·48 g.) which was recrystallised from ethanol when it showed m. p. and mixed m. p. 214°.

(iii) tert.-*Butyl xanthhydryl peroxide.* A solution of *tert.*-butyl xanthhydryl peroxide (1·0 g.) and sodium toluene-*p*-sulphinate (0·80 g.) in acetic acid (10 c.c.) at 50° immediately began to deposit crystals of *p*-tolyl xanthhydryl sulphone. After 1 hr., water (15 c.c.) was added yielding more sulphone (from ethanol; in all, 1·06 g., 86%), m. p. and mixed m. p. 214—215°. The filtrate, after being neutralised with sodium hydrogen carbonate, was extracted with light petroleum, yielding *tert.*-butyl hydroperoxide, which was identified as 1-*tert.*-butyl hydrogen 1-monoperphthalate (from ether–light petroleum; 50 mg.), m. p. and mixed m. p. 102—103°.

(iv) tert.-*Butyl triphenylmethyl peroxide.* On the addition of one drop of concentrated sulphuric acid to a solution of *tert.*-butyl triphenylmethyl peroxide (50 mg.) and sodium toluene-*p*-sulphinate (50 mg.) in acetic acid (5 c.c.), a yellow colour developed. After 1·5 hr. crystals began to separate. Next day these were filtered off (50 mg.) and recrystallised from benzene–light petroleum, yielding *p*-tolyl triphenylmethyl sulphone, m. p. and mixed m. p. 173—174°.

(v) *Bis*(*di*-p-*methoxyphenylmethyl*) *peroxide.* A red solution of the peroxide (0·20 g.) in glacial acetic acid (3 c.c.) containing one drop of concentrated sulphuric acid, was added to sodium toluene-*p*-sulphinate (0·20 g.) in acetic acid (2 c.c.); the colour slowly faded. After 45 min. the solution was poured over crushed ice, yielding di-*p*-methoxyphenylmethyl *p*-tolyl sulphone (from ethanol, 0·18 g.), m. p. and mixed m. p. 102—104°. In the absence of sulphuric acid, the peroxide was recovered from a similar reaction mixture after 1 hr.

(vi) tert.-*Butyl* 1-*methyl*-1-*phenylpropyl peroxide.* The peroxide (2·22 g., 1 mol.) which is insoluble in acetic and formic acids, was stirred with a solution of sodium toluene-*p*-sulphinate (1·78 g., 1 mol.) in 90% formic acid (50 c.c.) for 8 hr., the solution becoming homogeneous. After a further 48 hr. the mixture was poured over ice, yielding an oil which solidified. Recrystallisation from aqueous methanol yielded 1-methyl-1-phenylpropyl *p*-tolyl sulphone (0·98 g.), m. p. and mixed m. p. 65°.

(vii) 1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyl hydroperoxide.* After 16 hr. a solution of the hydroperoxide (0·5 g.) and sodium toluene-*p*-sulphinate (0·7 g.) in 98% formic acid (10 c.c.) had deposited a buff-coloured precipitate which did not melt below 300° and was insoluble in the common organic solvents but dissolved in water; from its aqueous solution the parent acid could be obtained by acidification; it was thus probably the acid decomposition product of the peroxide, *γ-o*-hydroxyphenylbutyric acid. The filtrate, on treatment with water, yielded toluene-*p*-sulphonic acid (0·10 g.), m. p. 104—105°. The hydroperoxide had thus apparently been reduced by the sulphinate. From a neutral solution the reduction product was isolated: a suspension of the hydroperoxide (2·0 g.) in a solution of sodium toluene-*p*-sulphinate (4·2 g.) in water (30 c.c.) was shaken for 5 hr. From the mixture, an oil was isolated with b. p. 92—94°/0·3 mm. (0·25 g.), which was identified as 1 : 2 : 3 : 4-tetrahydro-1-naphthol by the preparation of its hydrogen phthalate, m. p. and mixed m. p. 112°. No sulphone was isolated, but an undistillable viscous residue was obtained, which was probably polymerised 1 : 2-dihydronaphthalene.

(viii) 1-*Methyl*-1-*phenylpropyl hydroperoxide.* A solution of 1-methyl-1-phenylpropyl hydroperoxide (0·30 g.) and sodium toluene-*p*-sulphinate (0·42 g., 1 mol.) in 98% formic acid (13 c.c.), after 20 hr. was poured over ice, and the resulting emulsion neutralised with dilute sodium hydroxide. An ethereal extract yielded a colourless oil (0·14 g.), b. p. 102°/14 mm., identified as 1-methyl-1-phenylpropanol as follows. The oil (0·14 g.) was heated with 1-naphthyl *iso*cyanate (0·14 g.) in ligroin (5 c.c.) for 1 hr., and the whole filtered hot. On cooling, crystals separated, which were recrystallised from light petroleum (b. p. 60—80°), yielding 1-methyl-1-phenylpropyl 1-naphthylurethane, m. p. and mixed m. p. 128—129°. Hawkins (*J.*, 1949, 2076) reports m. p. 129—130·5°. We are indebted to Dr. E. G. E. Hawkins for the details of this reaction.

Reaction between Xanthhydryl Peroxide and Urea.—A suspension of the peroxide (0·181 g.) in a solution of urea (0·20 g., excess) in glacial acetic acid (30 c.c.) became homogeneous after 2 min. at 70°. After 3 days at room temperature, water (150 c.c.) was added and the

precipitated material filtered off through a weighed sintered-glass filter and washed with water (100 c.c.), giving *s*-dixanthhydrylurea (0·182 g., 94%), m. p. and mixed m. p. 270—272°. Titration of the combined filtrate and washings with standard potassium permanganate solution showed it to contain 96% of the theoretical amount of hydrogen peroxide.

Reaction between Xanthhydryl Peroxide and Ethyl Acetoacetate.—After 45 min. a solution of xanthhydryl peroxide (0·20 g.) and ethyl acetoacetate (0·26 g.) in acetic acid (5 c.c.) containing concentrated sulphuric acid (0·05 c.c.) was poured on ice, yielding ethyl xanthhydrylacetoacetate (from light petroleum; 0·34 g.), m. p. and mixed m. p. 88—89°.

Reaction between Xanthhydryl Peroxides and Acetone.—(i) tert.-*Butyl xanthhydryl peroxide.* A solution of *tert.*-butyl xanthhydryl peroxide (0·7 g.) in acetone (4 c.c.) containing concentrated sulphuric acid (0·1 c.c.), rapidly became deep red. After 60 hr. the mixture was poured over ice, yielding xanthhydrylacetone (from aqueous ethanol; 0·68 g.), m. p. 101—102° (Found: C, 80·8; H, 6·1. Calc. for $C_{16}H_{14}O_2$: C, 80·6; H, 5·9%). Fosse and Robyn (*Bull. Soc. chim.*, 1906, **35**, 1013) report m. p. 101—102° for this compound prepared by the hydrolysis of ethyl xanthhydrylacetoacetate.

(ii) tert.-*Amyl xanthhydryl peroxide.* Similarly, after 40 hr., a solution of *tert.*-amyl xanthhydryl peroxide (1·0 g.) in acetone (3 c.c.) containing concentrated sulphuric acid (0·05 c.c.) yielded xanthhydrylacetone (1·05 g.) which, recrystallised from aqueous ethanol, had m. p. and mixed m. p. 101—102° (Found: C, 80·8; H, 5·7%).

Disproportionation of Xanthhydryl Hydroperoxide.—Xanthhydryl hydroperoxide (0·98 g.) was warmed at 50° in glacial acetic acid (10 c.c.), and the mixture diluted with water, yielding xanthhydryl peroxide (from ethanol; 0·72 g.) as white needles, m. p. 152—153° (Found: C, 78·8; H, 4·8. Calc. for $C_{26}H_{18}O_4$: C, 79·2; H, 4·6%).

Grateful acknowledgment is made to the Chemical Society for a grant, and to Messrs. Laporte Chemicals Ltd., Luton, for the gift of hydrogen peroxide and *tert.*-butyl hydroperoxide. The authors thank Dr. R. F. Mason for carrying out the reactions of xanthhydrol with trialkyloxybenzenes.

CHEMISTRY DEPARTMENT, BATTERSEA POLYTECHNIC, LONDON, S.W.11.
WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, February 8th*, 1954.]

12-*Oxygenated Pregnane Derivatives. Part II.** *Preparation of* 21-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12 : 20-*trione from Hecogenin.*

By (MRS.) W. J. ADAMS, D. N. KIRK, D. K. PATEL, V. PETROW, and (MRS.) I. A. STUART-WEBB.

[Reprint Order No. 5110.]

An attempt to convert hecogenin into 21-acetoxy-17α-hydroxypregn-4-ene-3 : 12 : 20-trione is recorded. No difficulty was experienced in preparing 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X) from (I). Introduction of the 4 : 5-unsaturated linkage into (X), however, could not be effected.

THE conversion of deoxycholic acid into 12α : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (21-acetate), an analogue of *epi*hydrocortisone(*epi*cortisol), was recorded in Part I.* The present communication describes further experiments having as their object the conversion of hecogenin acetate (I) into 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X) and thence into 17α : 21-dihydroxypregn-4-ene-3 : 12 : 20-trione (21-acetate), the 12-oxygenated analogue of cortisone (acetate).

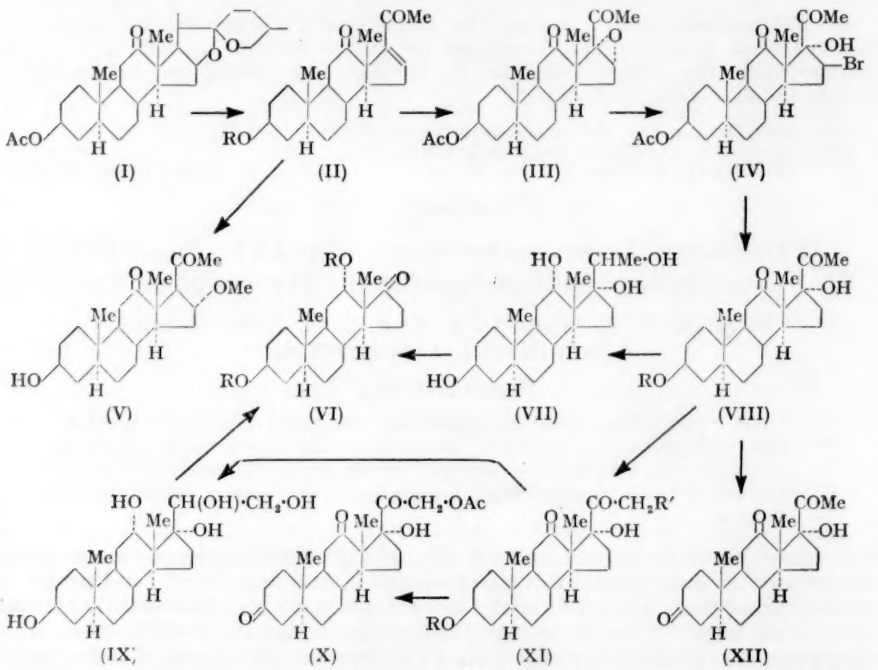
Hecogenin acetate (I) was readily degraded to 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = Ac) by methods developed by Marker and Rohmann (*J. Amer. Chem. Soc.*, 1940, **62**, 518) and Wagner, Moore, and Forker (*ibid.*, 1950, **72**, 1856). It was first converted into *ψ*-hecogenin diacetate which passed smoothly on oxidation with chromic acid into 3β-acetoxy-16β-(δ-acetoxy-γ-methylvaleroxy)*allo*pregnane-12 : 20-dione;

* Part I, *J.*, 1954, 1825.

careful hydrolysis of this "hecone diacetate" with aqueous-ethanolic potassium carbonate, followed by acetylation of the product, furnished (II; R = Ac).

Conversion of 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = Ac) into 3β : 17α-dihydroxy*allo*pregnane-12 : 20-dione (VIII; R = H) followed the general pattern established in Part I. Epoxidation of (II; R = Ac) with hydrogen peroxide in aqueous-methanolic sodium carbonate (Kendall, *J. Biol. Chem.*, 1952, **194**, 237) gave 3β-acetoxy-16α : 17α-epoxy*allo*pregnane-12 : 20-dione (III) * in 85% yield. Reaction of the last compound with hydrogen bromide in chloroform–acetic acid at −18° led smoothly to 3β-acetoxy-16β-bromo-17α-hydroxy*allo*pregnane-12 : 20-dione (IV) † (cf. however, Experimental section). Bromine was then readily removed by catalytic reduction over 2% palladium–calcium carbonate (cf. Part I), 3β-acetoxy-17α-hydroxy*allo*pregnane-12 : 20-dione (VIII; R = Ac) being obtained, which was smoothly hydrolysed to the diol (VIII; R = H).

The 3β-acetate so obtained had m. p. 131—133°, $[\alpha]_D^{26}$ +55°. It thus differs from the compound, m. p. 176°, $[\alpha]_D^{30}$ +117°, prepared by Mueller *et al.* by reducing (IV) with Raney nickel in ethanol or with zinc in acetic acid and also assigned structure (VIII; R = Ac). The formulation of our material as (VIII; R = Ac), however, is unequivocally established by the transformations described below. We therefore attempted to prepare the product, m. p. 176°, for structural studies but without success. In our hands reduction of (IV) with Raney nickel (prepared at 110° as described by Adkins, "Reactions of Hydrogen," Univ. Wisconsin Press, Wisconsin, 1937) in ethanol led only to authentic (VIII; R = Ac), m. p.



131—133°, whilst treatment with zinc dust in acetic acid furnished 3β-acetoxy*allo*pregnane-12 : 20-dione as the sole isolatable product (cf. Part I, section D).

An alternative approach to (VIII; R = H), *via* (II; R = H), was also examined. An attempt to hydrolyse (II; R = Ac) with aqueous-methanolic potassium carbonate, how-

* Cf. the paper by Mueller, Stobaugh, and Winniford (*J. Amer. Chem. Soc.*, 1953, **75**, 4888) which appeared after completion of Part II and in which the preparation of (II; R = Ac), (III), and (IV) is independently recorded.

ever, led to 3β-hydroxy-16α-methoxy*allo*pregnane-12 : 20-dione (V) admixed with only 10% of 3β-hydroxy*allo*pregn-16-ene-12 : 20-dione (II; R = H). As aqueous-methanolic potassium carbonate smoothly converts 3α : 12α-diacetoxypregn-16-en-20-one into the 3α-hydroxy-compound without concomitant addition of methanol to the double bond (Part I), the behaviour of (II) must be related to the polar effect of the adjacent 12-carbonyl group on the reactivity of the 20-keto-16 : 17-unsaturated system (see also Mueller *et al.*, *loc. cit.*).

The constitution assigned to (VIII; R = Ac) was confirmed as follows: (*a*) Dehydration with phosphorus oxychloride in pyridine (Reichstein, *Helv. Chim. Acta*, 1940, **23**, 170; 1941, **24**, 401) gave 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = Ac) identical with an authentic specimen (Wagner, Moore, and Forker, *loc. cit.*). Dehydration by Darzens's method surprisingly failed to yield (II; R = Ac), an abnormal product, $C_{23}H_{34}O_6S$, insoluble in sodium hydrogen carbonate solution, being formed. This result stands in contrast to the successful dehydration of 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one to the 16-ene recorded in Part I. (*b*) Reduction with sodium borohydride yielded *allo*pregnane-3β : 12α : 17α : 20-tetrol (VII; R = H), and subsequent oxidation with sodium bismuthate (Norymberski, *Biochem. J.*, 1953, **55**, 371) and acetylation gave 3β : 12α-diacetoxyandrostan-17-one (VI; R = Ac) (see p. 2213 for evidence regarding the configuration at $C_{(12)}$). Hydrolysis of the last compound gave 3β : 12α-dihydroxyandrostan-17-one (VI; R = H) which was oxidised by *N*-bromoacetamide in aqueous *tert.*-butanol to a diketo-alcohol, tentatively formulated as 12α-hydroxyandrostane-3 : 17-dione.

Before proceeding with the next stage of the partial synthesis, *i.e.*, the introduction of a 21-acetoxy-group into (VIII; R = H), we examined the conversion of this compound into 17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (XII) and confirmed that this was readily effected with *N*-bromoacetamide in aqueous *tert.*-butanol. The way was thus open to the preparation of 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X).

Monobromination of (VIII; R = H) in chloroform in the presence of hydrogen bromide gave the monobromo-compound (XI; R = H, R′ = Br), which passed into the corresponding acetoxy-derivative on treatment with sodium iodide in acetone, followed by reaction of the iodo-compound *in situ* with potassium hydrogen carbonate–acetic acid (1 : 1). The constitution of 21-acetoxy-3β : 17α-dihydroxy*allo*pregnane-12 : 20-dione (XI; R = H, R′ = OAc) has been assigned to this product. Its alternative formulation as the 11ξ-acetoxy-derivative of (VIII; R = H) is excluded because reduction with borohydride gives *allo*pregnane-3β : 12α : 17α : 20ξ : 21-pentol (IX) which passes into 3β : 12α-diacetoxyandrostan-17-one (VI; R = Ac) on oxidation with sodium bismuthate followed by acetylation. Acetylation of (XI; R = H, R′ = OAc) gave the 3β : 21-diacetate (XI; R = Ac, R′ = OAc), also prepared directly from (VIII; R = Ac).

N-Bromoacetamide in aqueous *tert.*-butanol oxidised (XI; R = H, R′ = OAc) to 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X). Attempts to effect the last stage of the partial synthesis by converting (X) into the Δ^4-derivative by the standard bromination–dehydrobromination techniques, however, were unsuccessful.

Experimental

Optical rotations were measured in $CHCl_3$ in a 1-dm. tube unless otherwise stated.

3β-*Hydroxy*allo*pregn*-16-*ene*-12 : 20-*dione* (II; R = H).—3β-Acetoxy*allo*pregn-16-ene-12 : 20-dione (2 g.) (Wagner, Moore, and Forker, *loc. cit.*) in methanol (65 ml.) was heated with potassium carbonate (400 mg.) and water (5 ml.) under reflux for 1 hr. The product (1·7 g.), isolated with ether, was chromatographed in benzene on alumina (50 g.; B.D.H., chromatography grade). Final acetone–ether and acetone eluates yielded 3β-*hydroxy*allo*pregn*-16-*ene*-12 : 20-*dione*, m. p. 210—211°, $[\alpha]_D^{24}$ +156° (*c*, 0·416) (Found: C, 76·7; H, 8·9. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·1%), after crystallisation from acetone–hexane. Reacetylation gave (II; R = Ac).

Early ether–acetone eluates yielded 3β-*hydroxy*-16α-*methoxy*allo*pregnane*-12 : 20-*dione* (V) (*ca.* 300 mg.), m. p. 142°, $[\alpha]_D^{25}$ +132° (*c*, 0·374) (Found: C, 73·1; H, 8·9. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·4%), after crystallisation from acetone–hexane.

3β-*Acetoxy*-16α : 17α-*epoxy*allo*pregnane*-12 : 20-*dione* (III).—(II; R = Ac) (2·5 g.) in methanol (310 ml.) was treated at 0° with water (37·5 ml.), 5% sodium carbonate solution

(5 ml.), and hydrogen peroxide (30 ml. of 30%). After 12 hr. at this temperature, water (300 ml.) was added, followed by dilute acetic acid until the mixture was neutral, and the mixture left at 0° for 16 hr. The separated solids on crystallisation from acetone and from chloroform–ether yielded 3β-acetoxy-16α : 17α-epoxy*allo*pregnane-12 : 20-dione, prisms, m. p. 235—237°, $[\alpha]_D^{26}$ +109° (*c*, 0·574) (Found : C, 71·4; H, 8·0. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·2%). Mueller *et al.* give m. p. 234—235°, $[\alpha]_D^{32}$ +103° in dioxan.

3β-*Acetoxy*-16β-*bromo*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (IV).—The foregoing compound (2·3 g.) in chloroform (48 ml.) was treated at −20° with acetic acid (18 ml.) and hydrogen bromide (5 ml. of a saturated solution in acetic acid). After storage at 0° the product was isolated with ether and crystallised from chloroform–ether. 3β-Acetoxy-16β-bromo-17α-hydroxy*allo*pregnane-12 : 20-dione formed prismatic needles, m. p. 163—165° or 174—176°, $[\alpha]_D^{25}$ +8° (*c*, 0·74) (Found : C, 58·8; H, 6·9; Br, 16·9. Calc. for $C_{23}H_{33}O_5Br$: C, 58·8; H, 7·0; Br, 17·1%). Mueller *et al.* give m. p. 176—178°, $[\alpha]_D^{30}$ +39° in EtOH.

3β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (VIII; R = Ac).—(i) The bromohydrin (12 g.) was reduced over 2% palladium–calcium carbonate (25 g.) in aqueous methanol (600 ml. ; 1 : 9). The crude product, after acetylation, was filtered in benzene through a short column of alumina and subsequently purified from hexane. 3β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* formed needles, m. p. 131—133°, $[\alpha]_D^{26}$ +55° (*c*, 0·57) (Found : C, 70·6; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%).

(ii) The bromohydrin (500 mg.) in ethanol (25 ml.) was stirred with Raney nickel (3 g.) on a steam-bath for 5 hr. The solution was filtered and concentrated, and the residue crystallised from ether–hexane. 3β-Acetoxy-17α-hydroxy*allo*pregnane-12 : 20-dione was obtained as needles, m. p. 131—132° not depressed on admixture with a sample prepared by (i) above.

(iii) The bromohydrin (500 mg.) in acetic acid (40 ml.) was stirred with zinc dust (1 g.) on a steam-bath for 4 hr. The cooled solution was diluted with ether, filtered, and washed until neutral. From the crude product, after several recrystallisations from aqueous ethanol, 3β-acetoxy*allo*pregnane-12 : 20-dione was obtained, having m. p. and mixed m. p. 182—187° (Found : C, 73·7; H, 9·2. Calc. for $C_{23}H_{34}O_4$: C, 73·8; H, 9·1%). It was recovered unchanged after attempted acetylation.

3β-*Acetoxy*allo*pregnane*-12 : 20-*dione*.—3β-Acetoxy*allo*pregn-16-ene-12 : 20-dione (1·86 g.) was reduced over 1% palladium–calcium carbonate (1 g.) in methanol (70 ml.). By crystallisation of the product from acetone 3β-acetoxy*allo*pregnane-12 : 20-dione was obtained, having m. p. 190—192°, $[\alpha]_D^{25}$ +138° (*c*, 0·508) (Found : C, 74·2; H, 9·3%). Mueller *et al.* give m. p. 189—190°, $[\alpha]_D^{29}$ +139°.

3β : 17α-*Dihydroxy*allo*pregnane*-12 : 20-*dione* (VIII; R = H), prepared by hydrolysing the compound (VIII; R = Ac) with ethanolic sodium hydroxide at room temperature, or with aqueous-methanolic potassium carbonate under reflux for 1½ hr., formed prisms, m. p. 204—207°, $[\alpha]_D^{22}$ +71° (*c*, 0·51) (Found : C, 72·9; H, 9·5. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%), after crystallisation from acetone.

Dehydration of (VIII; R = Ac) (1 g.) in pyridine (6 ml.) with phosphorus oxychloride (1 ml.) at 135° for 45 min. led to 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione, m. p. 179—181° alone or on admixture with an authentic specimen (see above). Dehydration by Darzens's method gave a *product*, plates, m. p. 169—170° (Found : C, 63·5; H, 7·3; S, 7·3. $C_{23}H_{34}O_6S$ requires C, 63·1; H, 7·7; S, 7·3%), after crystallisation from acetone–ether.

Reduction of (VIII; R = H).—The diketone (3·48 g.) in methanol (50 ml.) was reduced with sodium borohydride (400 mg.) in methanol (10 ml.). After acetylation, purification of the product yielded a *diacetate*, needles, m. p. 228—230°, $[\alpha]_D^{25}$ +25° (*c*, 0·406) (Found : C, 68·6; H, 9·3. $C_{25}H_{40}O_7$ requires C, 68·8; H, 9·2%).

3β : 12α-*Diacetoxyandrostan*-17-*one* (VI; R = Ac).—The foregoing diacetate (1·3 g.) was hydrolysed in aqueous methanol (50 ml.; 1 : 9) with potassium hydroxide (2·5 g.) for 1 hr. under reflux and the product (m. p. 236—240°; 930 mg.) was treated with sodium bismuthate (5 g.) in 50% acetic acid (100 ml.) (Norymberski, *loc. cit.*). Acetylation of the oxidised material gave 3β : 12α-*diacetoxyandrostan*-17-*one*, needles, m. p. 197—199°, $[\alpha]_D^{25}$ +137° (*c*, 0·406) (Found : C, 70·4; H, 8·2. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·7%), after crystallisation from aqueous methanol.

3β : 12α-*Dihydroxyandrostan*-17-*one* (VI; R = H), prepared by hydrolysing the foregoing compound (950 mg.) in aqueous methanol (50 ml. ; 1 : 9) with potassium hydroxide (1 g.) under reflux for 1 hr., formed needles, m. p. 195—197°, $[\alpha]_D^{22}$ +147° (*c*, 0·436) (Found : C, 74·7; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·8%), after crystallisation from acetone. The compound gave a positive Zimmermann reaction for the 17-keto-group.

Configuration at $C_{(12)}$.—(i) $[M]_D$ of (VI; R = Ac) $-[M]_D$ of 3β-acetoxyandrostan-17-one = +274°. Molecular rotation increment of 12α-OAc = +280°, 12β-OAc = +76° (see Barton and Klyne, *Chem. and Ind.*, 1948, 755).

(ii) $[M]_D$ of (VI; R = H) $-[M]_D$ of 3β-hydroxyandrostan-17-one = +196°. Molecular rotation increment of 12α-OH = +93°, 12β-OH = +50°. Agreement is less satisfactory in this instance, presumably owing to vicinal action of the 17-keto-group.

12α-*Hydroxyandrostane*-3 : 17-*dione*.—3β : 12α-Dihydroxyandrostan-17-one (400 mg.) in *tert.*-butanol (15 ml.), kept with *N*-bromoacetamide (828 mg.) in water (1 ml.) for 16 hr. at room temperature, gave 12α-*hydroxyandrostane*-3 : 17-*dione*, m. p. 187—188°, $[\alpha]_D^{22}$ +221° (*c*, 0·462) (Found: C, 75·0; H, 9·2. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·2%). The presence of a hydroxyl group in this compound was revealed by its infra-red absorption spectrum and confirmed by conversion into the *acetate*, m. p. 200—202° (Found: C, 72·5; H, 9·0. $C_{21}H_{30}O_4$ requires C, 72·7; H, 8·7%).

17α-*Hydroxy*allo*pregnane*-3 : 12 : 20-*trione* (XII).—The diol (VIII; R = H) (6·4 g.) in *tert.*-butanol (150 ml.) was oxidised with *N*-bromoacetamide (4 g.) in water (7·5 ml.) for 16 hr. at room temperature. After precipitation with water, the product was collected, debrominated by brief treatment with zinc dust–acetic acid, and purified from chloroform–ether. 17α-*Hydroxy*allo*pregnane*-3 : 12 : 20-*trione* had m. p. 222—224°, $[\alpha]_D^{24}$ +79° (*c*, 0·454) (Found: C, 72·9; H, 8·4. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

21-*Bromo*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = H, R′ = Br).—The diol (VIII; R = H) (3·60 g.) in chloroform (50 ml.) was treated at room temperature with bromine in chloroform (87 ml.; 0·1204M) during 90 min. Bromination was slow even in the presence of hydrogen bromide. Purification of the product from chloroform–ether gave 21-*bromo*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-dione, m. p. 183—184°, $[\alpha]_D^{24}$ +57° (*c*, 0·50) (Found: C, 61·5; H, 7·6; Br, 15·7. $C_{21}H_{31}O_4Br$ requires C, 59·0; H, 7·2; Br, 18·7%), which decomposed on storage.

21-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = H, R′ = OAc).—The foregoing bromo-compound (3·15 g.) in acetone (102 ml.) was treated with sodium iodide (1·8 g.) for 20 min. under reflux under nitrogen. After filtration to remove sodium bromide, the solution was poured on sodium hydrogen carbonate (15 g.) admixed with acetic acid (9 ml.), and refluxing under nitrogen was continued for a further 16 hr. After removal of acetone the product was extracted with ether and crystallised from acetone–hexane. 21-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-*dione* formed needles, m. p. 206—209°, $[\alpha]_D^{23}$ +50° (*c*, 0·52) (Found: C, 68·2; H, 8·4. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

Reduction of (XI; R = H, R′ = OAc) with sodium borohydride, followed by oxidation of the total reduction product [presumably (IX)] with sodium bismuthate, and acetylation, furnished 3β : 12α-diacetoxyandrostan-17-one, m. p. 197—199°, alone or on admixture with a sample prepared from (VII; R = H) (above).

3β-*Acetoxy*-21-*bromo*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = Ac, R′ = Br), prepared by bromination of (VIII; R = Ac), had m. p. 172—174° (softening at 168°) (Found: C, 58·2; H, 6·8; Br, 17·7. $C_{23}H_{33}O_5Br$ requires C, 58·8; H, 7·0; Br, 17·1%).

3β : 21-*Diacetoxy*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = Ac, R′ = OAc).—(i) Prepared from the foregoing compound, the *product* formed needles, m. p. 161—163°, $[\alpha]_D^{23}$ +41° (*c*, 0·53) (Found: C, 66·7; H, 7·9. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·0%), after crystallisation from acetone–hexane; (ii) prepared by acetylation of (XI; R = H, R′ = OAc), the compound had m. p. 161—163°, not depressed on admixture with a sample prepared as in (i) (above).

21-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12 : 20-*trione* (X).—The diacetate (XI; R = H, R′ = OAc) (4·06 g.) in *tert.*-butanol (120 ml.) was treated at room temperature with water (4 ml.) and *N*-bromoacetamide (2·76 g.). After being shaken for 5 hr. in absence of light, the mixture was poured into water, and the product isolated with ether and debrominated with zinc dust (3·5 g.) in acetic acid (15 ml.) for 15 min. on the water-bath. 21-*Acetoxy*-17α-*hydroxy*allo-*pregnane*-3 : 12 : 20-*trione* had m. p. 207—210°, $[\alpha]_D^{26}$ +66° (*c*, 0·482) (Found: C, 68·9; H, 8·1. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·9%), after purification from acetone–ether. The compound depressed the m. p. of (XI; R = H, R′ = OAc).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, February 11th*, 1954.]

The Separation and Purification of Americium-241 and the Absorption Spectra of Tervalent and Quinquevalent Americium Solutions.

By G. R. Hall and P. D. Herniman.

[Reprint Order No. 5049.]

The separation and purification of americium-241 (25 mg.), produced by the β-decay of plutonium-241 in plutonium containing small amounts of the latter isotope, is described.

The absorption spectra of americium(III) in perchloric acid and in hydrochloric acid have been measured. The narrow 504-mμ peak does not obey either Beer's or Lambert's law; the 814-mμ peak obeys both.

By following changes in the absorption spectra the disproportionation and self-reduction of americium(V) in hydrochloric acid have been observed. Self-reduction is caused by reducing materials produced in solution by α-particle bombardment. In low acid concentrations only self-reduction occurs, but in more concentrated acid solutions disproportionation predominates.

The Separation and Purification of Americium by Carrier-free Methods.—Americium-241 is the β-decay product of plutonium-241, whose half life is 13·0 ± 0·2 years (MacKenzie, Lounsbury, and Boyd, *Phys. Review*, 1953, **90**, 327). Plutonium-241 is formed from uranium-238 in a nuclear reactor by the series of reactions:

$$U^{238} \xrightarrow{n\gamma} U^{239} \xrightarrow{\beta} Np^{239} \xrightarrow{\beta} Pu^{239} \xrightarrow{n\gamma} Pu^{240} \xrightarrow{n\gamma} Pu^{241} \xrightarrow{\beta} Am^{241}$$

As plutonium-241 is the product of three successive neutron captures, the quantity formed, compared with plutonium-239, is small except for long irradiations. The separation of americium from irradiated uranium would be extremely difficult because of the enormous activities of the fission products, especially as compounds of the stable valency, americium(III), are isomorphous with the corresponding rare-earth compounds which comprise an appreciable fraction of the total fission products. It is more convenient to start from partially purified plutonium, free from fission products, containing reasonable amounts of plutonium-241. If this is allowed to decay for a suitable period the americium can be extracted by using only glove-box handling techniques. Remote handling methods are necessary if fission products are present.

The 10 mg. of americium used for the absorption-spectra measurements were extracted from many grams of plutonium. Precipitation of the plutonium as plutonium(IV) peroxide separated most of the plutonium from the americium which is not precipitated (Milsted, 1953, H.M.S.O., A.E.R.E., report C/R 1102). The supernatant liquor contained small amounts of plutonium, uranium, and iron, and all the americium, and provided the starting material for the separations which are described.

Americium-241 is an α-emitter. Its half-life of 470 years (Harvey, *Phys. Review*, 1950, **85**, 482) corresponds to a specific activity of $7{\cdot}0 \times 10^6$ α-particles/min./μg. There are also some soft electromagnetic radiations (Beling, Newton, and Rose, *Phys. Review*, 1952, **86**, 797) with a particularly abundant 60 kev radiation (0·40 per α-particle).

Although the chemical properties of uranium, plutonium, and americium are similar there is an increasing tendency for lower valency states to become the most stable. In uranium the sexavalent state, the uranyl ion, is difficult to reduce whereas in plutonium each valency from three to six can readily be prepared. Plutonium(IV) disproportionates in solution at a rate inversely proportional to about the fourth power of the hydrogen-ion concentration (Connick and McVey, University of California Radiation Laboratory report UCRL 1687). Plutonium(III) is stable in non-oxidising acids but can be produced in dilute nitric acid solution only if a large excess of reducing agent is present. Plutonium(VI) is readily prepared by oxidation of plutonium(IV), *e.g.* with hot sodium dichromate solution. Americium(III) is stable in all acids and americium(VI) is produced only with great difficulty. Americium(V) is prepared by oxidation with sodium hypochlorite but disproportionates

in moderately strong acid. The transuranium elements can be separated by means of this gradation in valency stability. Thus, if a mixture of uranium, plutonium(III), and americium (III) is treated with hot sodium dichromate, the americium(III) can be precipitated as trifluoride, while the uranyl and plutonyl fluorides remain in solution.

The isolation and separation of americium as a tracer and on the microgram scale have been reported by Thompson, Morgan, James, and Perlman ("The Transuranium Elements," McGraw Hill, New York, 1949, Vol. II, p. 1339), by Cunningham (*ibid.*, p. 1363) and by Milsted (*loc. cit.*).

Experimental

Removal of Plutonium by Solvent Extraction.—After the peroxide precipitation, the stock solution contained plutonium (~2 g.), iron (500 mg.), uranium (500 mg.), americium (~25 mg.) in 100 ml. of 0·5M-nitric acid. Most of the plutonium was removed by the solvent extraction of plutonium-(IV) or -(VI); the solvents tributyl phosphate, "Dibutyl carbitol" (diethylene glycol di-*n*-butyl ether), or di*iso*butyl ketone are suitable. Some uranium is removed but americium(III) is not. The plutonium was extracted from the combined solvent phases by stirring with 5% hydroxylamine in 0·1M-nitric acid [to produce the solvent-insoluble tervalent plutonium(III)]. Counting sources were prepared from this solution and from the aqueous layer after the solvent extraction. These sources were examined in a pulse analyser (see p. 2216); the aqueous layer was found to contain ~23 mg. of americium together with 55 mg. of plutonium. The solvent retained 1·3 mg. of americium, carried over by poor separation of the solvent and aqueous phases.

Separation from Iron by Oxalate Precipitation.—Americium trioxalate is coprecipitated with plutonium tetraoxalate, whereas iron is soluble in oxalate solution (Milsted, *loc. cit.*). Accordingly, an excess of oxalic acid crystals was added to the aqueous layer and a brown precipitate of plutonium and americium oxalate was removed by centrifugation. The yellow supernatant liquid contained mainly iron, some uranium, and 0·25 mg. of americium. The oxalate precipitate was treated with hot concentrated sulphuric acid, a pink slurry of plutonium and americium sulphates being obtained which gradually dissolved on dilution with water. After the solution had cooled, ammonium hydroxide was slowly added, and americium trihydroxide and plutonium tetrahydroxide were coprecipitated. The supernatant liquid after centrifugation had high α-activity, but, as it showed only a low γ-activity, this was presumed to be due to plutonium in a soluble hydrolysed form.

Separation from Plutonium by "Oxidation and Fluoride Precipitation" Cycles.—The hydroxides were dissolved in nitric acid and the acidity adjusted to normality. Solid sodium dichromate was added, and the solution was heated at 90—95° for several hours. The solution, now containing americium(III) and plutonium(VI), was transferred to a nitrocellulose tube and treated with concentrated hydrofluoric acid. The resulting pink precipitate was washed with water and dissolved in concentrated nitric acid. Pulse analysis of a source prepared from this solution showed <3% of the α-activity to be due to plutonium. As the half life of plutonium-239, the principal isotope in this plutonium, is $2{\cdot}44 \times 10^4$ years, <40 mg. of plutonium were left; the dichromate oxidation of plutonium cannot have been complete. Spectrographic analysis of a solution containing 50 μg. of americium gave: chromium, 10; magnesium, 1; tin, <1 (limit); silicon, 10; iron, 0·8; aluminium, 100; calcium, 100 μg.

Final Purification.—The americium was precipitated as the pink gelatinous trihydroxide with a sufficient excess of potassium hydroxide solution to hold aluminium in solution as aluminate. The solubility of americium in the supernatant layer was <1 μg. per ml. The hydroxide was dissolved in hydrochloric acid and the precipitation repeated. The precipitate was again dissolved in hydrochloric acid and the pH of the solution was reduced to 2 by adding ammonium hydroxide. Solid ammonium sulphate was then added and a white precipitate of calcium sulphate was formed which was washed with dilute ammonium sulphate solution. The washings were added to the americium-containing layer, which was put through a final "oxidation–fluoride" cycle. Spectrographic analysis showed the calcium and aluminium impurities to be reduced to 10% (of the americium).

Final purification was achieved by an ion-exchange process described by Street and Seaborg (*J. Amer. Chem. Soc.*, 1950, **72**, 2790) in which americium was eluted from a Dowex-50 column with concentrated hydrochloric acid. Spectrographic analysis of this product gave the result: chromium and manganese, undetectable; silicon, 8; iron, 0·2; aluminium, 1·6%; calcium, undetectable. The silicon figure is probably incorrect; no other elements were detected.

A yield of 25 mg. of americium was obtained.

Estimation of Americium.—Pure americium solutions were estimated by α-particle counting. Sources were prepared on platinium discs and for most accurate work were counted in a low-geometry proportional methane chamber (Hurst and Hall, *Analyst*, 1952, **77**, 790).

If other α-emitters were present, *e.g.* plutonium in the first stages of the above separations, the α-pulses from the counting chamber were fed into a pulse analyser. The discriminating bias of the analyser channels was suitably adjusted to cover, in this case, an α-particle energy range of 5—6 Mev. The mean energies and half lives of the plutonium isotopes and americium are as follows:

Isotope	Half-life, yr.	α-Particle energy, Mev	Isotope	Half-life, yr.	α-Particle energy, Mev
Plutonium-238	90·0	5·47	Plutonium-240	6000	5·15
Plutonium-239	24,400	5·14	Americium-241	470	5·47

The pulse analyser will not discriminate between the α-particles of plutonium-238 and americium or those of plutonium-239 and -240. Hence two peaks are observed in the curve of α-particle abundance against α-particle energy, and it is necessary to know the plutonium-238 content of the plutonium before the actual amount of americium can be calculated.

Although α-pulse analysis provides a convenient method of estimating americium in plutonium, it is difficult to measure less than a few units % by weight of plutonium in americium. This is because of the large difference in the half-lives of americium and plutonium. A better method is to oxidise the plutonium to plutonyl ion and measure the absorption of the 833-mμ plutonyl peak spectrophotometrically. As little as 0·5% of plutonium in 25 mg. of americium can thus be detected. It is possible that the plutonium in americium could be estimated by activation analysis, the fission cross-sections being 664 and 3 barns, respectively.

During each stage of the purification the americium was conveniently followed by means of its γ-radiation, a thin-window Geiger tube being used. After each precipitation, the solution was centrifuged and a little of the supernatant liquid was withdrawn in a fine glass tube and held near the Geiger tube. The monitor response gave an approximate figure for the americium in the solution.

Spectrophotometry of Americium Solutions.—Many workers have described the absorption spectra of americium in solution but most of the measurements have been made with very small quantities. Recently Stephanou, Nigon, and Penneman (*J. Chem. Phys.*, 1953, **21**, 42) have reported the absorption spectra of americium-(III), -(V), and -(VI) in 0·1M-perchloric acid with americium concentrations of 1—3 g./l. Asprey, Stephanou, and Penneman (*J. Amer. Chem. Soc.*, 1951, **73**, 5715) reported the preparation and absorption spectra of americium(VI) solutions at similar concentrations, and Werner and Perlman (U.S. Atomic Energy Commission Report A.E.C.D. 2898) that of americium(V) solutions.

The spectrum of each valency state possesses a few very sharp absorption bands. Stephanou *et al.* (*loc. cit.*) find that the 504-mμ band of americium(III) does not obey the Beer–Lambert laws at high optical densities.

Further results on americium absorption spectra are reported below.

Experimental. All the previous purifications and the preparation of the spectrophotometer solutions were carried out in a large laboratory glove box in which a pressure slightly lower than atmospheric was maintained, and the usual radiochemical precautions were observed. A complete " Uvispek " spectrophotometer was contained in a separate glove box and the cell compartment was maintained at 25°. The high γ-ray flux from the americium did not affect the stability of the spectrophotometer.

All chemicals were of " AnalaR " grade. Water was redistilled from alkaline permanganate solution. Solutions were centrifuged before measurement in the spectrophotometer.

It was necessary to recover the americium after each experiment, as only 10 mg. were available for the following measurements.

Results and Discussion

Americium(III).—*Perchloric acid solutions.* Freshly precipitated americium trihydroxide was washed with water and dissolved in 0·1M-perchloric acid. The absorption spectrum was measured from 250 to 1000 mμ. Above 400 mμ the spectrum agreed well with those

reported by Stephanou *et al.* (*loc. cit.*) and by Stewart (AECD-3351). Below 400 mμ the intensity of absorption was found to be considerably greater than that reported by these authors, although the peaks appear at the same wave-lengths. It seems that the peaks are superimposed on a continuum of absorption increasing as the wave-length decreases. Stephanou found that absorption below 400 mμ gradually increased with time and suggested that this was due to the production of hydrogen peroxide by the reaction of α-particles with water. We found that absorptions below 400 mμ gradually decreased with time

FIG. 1. *Absorption spectra of* Am(III) *in* 0·1M-*perchloric acid.*

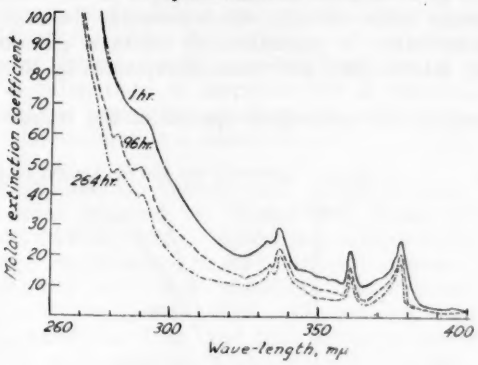
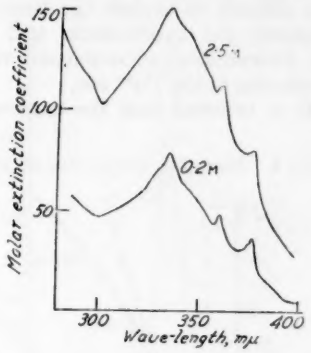


FIG. 2. *Absorption spectra of* Am(III) *in hydrochloric acid at lower wave-lengths.*



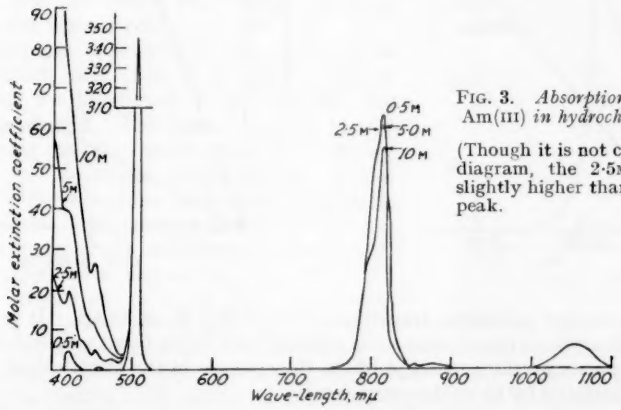


FIG. 3. *Absorption spectra of* Am(III) *in hydrochloric acid.*

(Though it is not clear in the diagram, the 2·5M peak is slightly higher than the 5·0M peak.

(Fig. 1), although the general structure remained the same. The absorption in the visible region at the two main peaks (504 and 814 mμ) remained unchanged during the 264 hr. in which the solution was examined, and hence no precipitation can have occurred.

The solution was made molar with respect to perchlorate ion by the addition of solid sodium perchlorate. This produced a small decrease in absorption—about 3% for the 377-mμ peak and 20% at 290 mμ. The spectrum of freshly-prepared americium(III) in M-perchloric acid is similar to that of the freshly prepared solution in 0·1M-acid but the absorption rises more steeply below 300 mμ.

This variable absorption at low wave-lengths is not due to hydrolysis, because the effect is enhanced by increasing the acidity both in perchloric acid and hydrochloric acid. There might be some impurity absorbing at lower wave-lengths, but it could not be detected. It is thus inadvisable to use the absorption peaks below 400 mμ for the analysis of americium(III).

Hydrochloric acid solutions. In hydrochloric acid similar relatively high ultra-violet absorptions are observed. The absorption in 0·2M-hydrochloric acid is considerably higher than that in 0·1M-perchloric acid and the peaks are less well defined. In 2·5M-hydrochloric acid the structure almost disappears, and as the acidity is increased the absorption extends to higher wave-lengths and reaches 400 mμ in 10M-acid (Figs. 2 and 3). The spectrum in the visible region shows little change even in concentrated acid. Thus the 1050-mμ peak remains unchanged in height and position, the 814-mμ peak is reduced, and the 504-mμ peak decreased slightly, when allowance is made for the failure of Beer's law. The small changes are probably caused by small changes in the electronic transition probabilities produced by the great increase in ionic strength of the solution. It is difficult to explain the large changes below 450 mμ, which resemble the effect of increasing the hydrochloric acid concentration of plutonium(IV) solutions (Hindman, U.S. Atomic Energy Commission report, MDDC 1257) and which is explained by chloride complexing of the Pu^{4+} ion.

It is believed that the narrow bands in the absorption spectra of the transuranic

FIG. 4. *Beer's law plot for* Am(III) *peaks.*

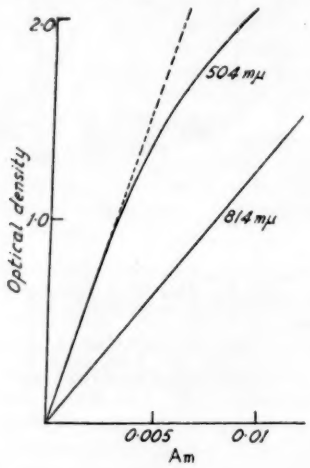
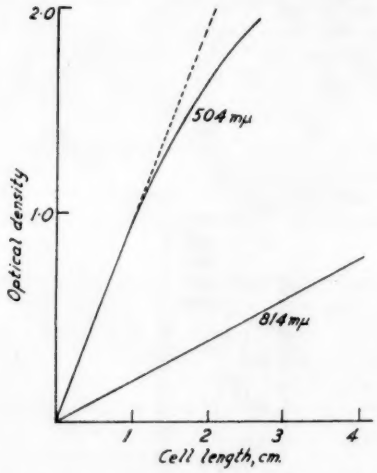


FIG. 5. *Lambert's law plot for* Am(III) *peaks.*



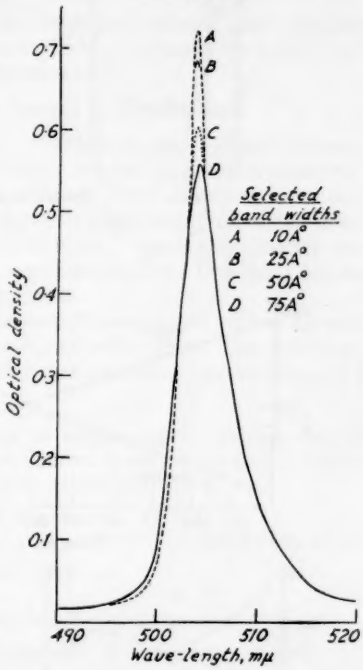
elements are due to the forbidden transitions of shielded *5f* electrons. It may be that the ultra-violet absorptions result from some allowed transitions to an unshielded electronic state; such transitions would be susceptible to the changes in the electric field around the americium ions produced by chloride complexing.

Beer's and Lambert's law. The 504-mμ peak is extremely narrow, and Stephanou *et al.* (*loc. cit.*) find Beer's and Lambert's law to fail at high optical densities (>1·7). To obtain further information on this for analytical purposes the following measurements were made. A concentrated stock of americium(III) in M-hydrochloric acid was prepared. The optical densities of several dilutions of this stock at the 504- and 814-mμ peaks were measured. For one solution the absorptions in 0·5, 1·0, 2·0 and 4·0 cm. cells were also measured. The results are plotted in Figures 4 and 5. Neither Beer's nor Lambert's law is obeyed for the 504-mμ peak, but both are obeyed for the broader 814-mμ peak. The failure may be due to two instrumental effects—(*a*) the spectrophotometer-selected band-width is too large for the narrow 504-mμ peak and (*b*) there may be some stray light interference which would be more serious at high optical densities. A calibration curve of optical density plotted against concentration for the similar narrow 833-mμ plutonyl $(PuO_2)^{++}$ peak shows these combined effects. The curve obtained by using a glass prism shows less deviation from Beer's law at high optical densities than a similar curve obtained

by using the quartz prism, because the glass prism provides appreciably greater dispersion than the quartz prism at this wave-length.

The 504-mμ americium peak has been plotted for several slit widths for ranges of optical density which can be measured with good accuracy (Fig. 6). The observed peak height increases for smaller selected band widths. This shows that the normal slit width, corresponding to a dispersion of 10 Å (Hilger "Uvispek" handbook), is not sufficiently small to measure the actual peak top. It follows that as higher optical densities are measured for a given band width the peak heights will become increasingly smaller than the true heights. This occurs in the present study. If there were no stray light interference (this could not be checked because no suitable filters were available), the above deviations would not occur in an instrument of sufficiently high resolution.

FIG. 6. *Effect of slit width on* Am(III) 504 *mμ peak.*



For estimations of americium(III) in solution the 504-mμ peak gives good results providing a Beer's law calibration is carried out at the slit width to be used.

Americium(V).—Americium(V) (AmO_2^+) solutions were prepared by Werner and Perlman's method (AECD 2898). Americium trihydroxide (10 mg.) was dissolved in 4M-potassium carbonate solution (2 ml.) and M-sodium hypochlorite solution (0·5 ml.) was added. The solution was heated at 95° for 1 hr. and then set aside overnight to ensure complete precipitation of the white americium carbonate which was washed and then dissolved in the desired acid.

The absorption spectrum of americium(V) in 0·5M-hydrochloric acid (Fig. 7) is very similar to that reported by Stephanou *et al.* (*loc. cit.*) for 0·1M-perchloric acid. The americium is slowly reduced, owing to the production of reducing species by the α-particle bombardment of the solution. The decrease in americium(V) and growth of americium(III), which were followed by measuring the absorptions at 715 and 514 mμ, respectively, were both linear with respect to time (Fig. 8), showing the reduction to be of zero order with respect to the individual ionic species. The slight curvature at zero time indicates an induction period while initial traces of oxidising impurities in the solution are destroyed. For a postulated rate law $d[Amv]/dt = k[Am]$ where [Am] is the total concentration, k is found to be 0·0074 hr.$^{-1}$, similar to the value of 0·023 hr.$^{-1}$ obtained by Asprey and Stephanou (AECD 924) for americium(V) in M-perchloric acid. These workers find the reduction to be of first order with respect to the total americium concentration for a concentration range 0·009—0·033 M. The mass balances obtained in our calculations for americium-(III) and -(V) show that not more than 3% of a possible americium(IV) ion can be present. It appears that if any is formed it is immediately decomposed in solution to americium(III). At higher acidities the americium(V) concentration is expected to decrease because of both α-particle-induced self-reduction and disproportionation.

For studies on the disproportionation of americium(V) in hydrochloric acid, information on the change of molar extinction coefficients with acidity was required. Absorptions of solutions of americium(V) in 2·5M- and 5M-hydrochloric acid at 514 and 715 mμ [and also 504 and 814 mμ for americium(III) and 992 mμ for americium(VI)] were measured at suitable time intervals. Extrapolation of the optical densities to zero time gave values of the molar extinction coefficients for pure americium(V) solution. The values for 0·1M-perchloric acid are those reported by Stephanou *et al.* (*loc. cit.*).

Absorption for both the americium(v) peaks drops considerably as the acidity is increased. The complete spectrum in 2·5M-hydrochloric acid (Fig. 7) shows a considerable increase in absorption from 400 to 450 mμ.

The change of americium valency with time in the 2·5M- and 5M-acid solutions has been calculated. Owing to insufficient readings at 992 mμ no americium(VI) was detected.

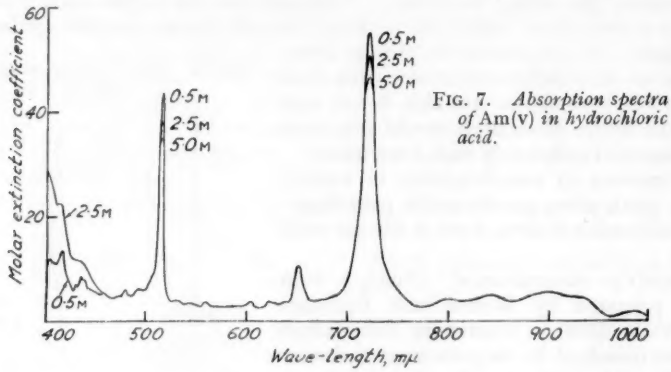


FIG. 7. *Absorption spectra of* Am(v) *in hydrochloric acid.*

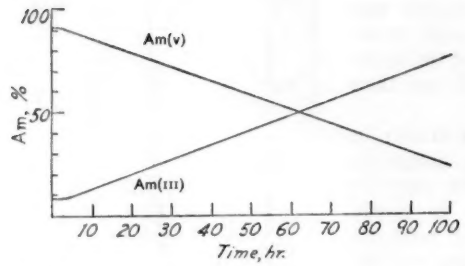


FIG. 8. *Self reduction of* Am(v) *in* 0·5M-*hydrochloric acid.*

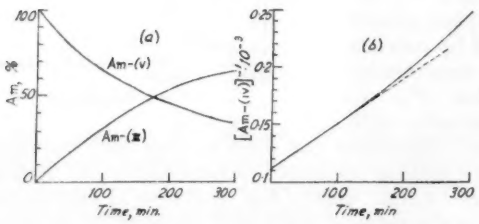


FIG. 9. *Reduction of* Am(v) *in* 5·0M-*hydrochloric acid.*

The mass balance between calculated quantities of americium-(v) and -(III) and the total americium concentration is such that <5% of americium(VI) could have been formed, the

Molar extinction coefficients for americium(v).

λ, mμ	0·1M-$HClO_4$	0·5M-HCl	2·5M-HCl	5M-HCl
514	45·6	44·4	39·1	35·7
715	59·3	56·4	51·9	47·4
814	—	~5	~4	~6

overall change being the conversion of americium-(v) into -(III). The reduction of the americium(v) in 2·5M-acid was slower than in 0·5M-acid, whereas in 5·0M-acid the reduction was faster than in either 0·5M- or 2·5M-acid.

The change of valency with time for the 5·0M-acid solution is plotted in Figure 9*a* and 1/[Am(v)] is plotted against time in Figure 9*b*. The latter curve is approximately linear at the beginning, indicating a bimolecular reaction, but then deviates upwards possibly

because some americium(V) is also being self-reduced. Similar curves were obtained in 2·5M-hydrochloric acid. The initial rates of reduction of the americium(V) for these two acidities were approximately dependent on the fourth power of the hydrogen-ion concentration.

It appears that as the hydrochloric acid concentration is increased the rate of self reduction of americium(V) decreases. This may be due to the reducing species being less stable, or the americium(V) becoming more stable, in more concentrated acid because of chloride complex-formation. The progressive drop in the molar extinction coefficients in going from 0·1M-perchloric acid to 0·5, 2·5, and 5·0M-hydrochloric acid is evidence for complex-formation. Also the rate constant for self-reduction (k) in 0·5M-hydrochloric acid is one third of its value in 0·1M-perchloric acid.

In 2·5M- and 5·0M-acid reduction appears to be by disproportionation since the rate is bimolecular with respect to americium(V) and varies as the fourth power of the hydrogen-ion concentration. Disproportionation could be represented by

$$2AmO_2^+ + 4H^+ = AmO_2^{2+} + Am(IV) + 2H_2O$$

We did not observe any americium-(IV) or -(VI). Stephanou, Asprey, and Penneman (U.S. Atomic Energy Commission Report AECU-925) suggest that americium(VI) is reduced to americium-(V) and -(III) in strong acid, although they observed some americium(VI) in their experiments on the disproportionation of americium(V) in perchloric acid. In our experiments the quartz prism used in the " Uvispek " spectrophotometer made measurement of the americium(VI) peak at 992 mμ very insensitive. Our mass balances are such that <5% americium(VI) could have been present.

In order to understand the decomposition of americium(V) solutions it will be necessary to separate these two modes of reduction. More information about the stability of americium-(IV) and -(VI) is required before satisfactory rate equations can be deduced for the disproportionation process.

The authors thank the Emission Spectroscopy Group for spectrographic analyses, and Mrs. K. M. Glover for carrying out pulse analyses. Acknowledgment is also made to the Director, Atomic Energy Research Establishment, for permission to publish this work.

CHEMISTRY DIVISION, ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, BERKS. [*Received, January 22nd,* 1954.]

The Cyclization of Substituted N-*Thiocarbamoylglycines, and Some* mero*Cyanine Dyes derived from the Products.*

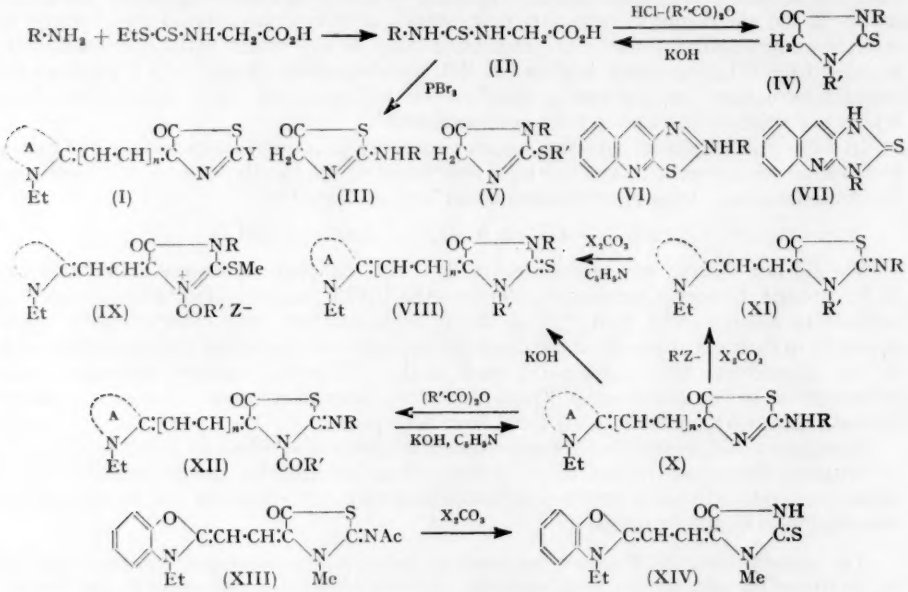
By R. A. JEFFREYS.

[Reprint Order No. 5067.]

It is shown that substituted *N*-thiocarbamoylglycines (II) cyclize to 2-thiohydantoins, 1-acyl-2-thiohydantoins, and 2-(secondary amino)thiazol-5-ones with mineral acid, acetic anhydride, and phosphorus tribromide respectively. The ultra-violet absorption spectra of 2-thiohydantoins and similar compounds are discussed. *mero*Cyanine dyes are prepared from all these intermediates, and both alkyl and acyl derivatives of thiazol-5-one dyes are described. The absorption maxima of various 2-substituted thiazol-5-one dimethin*mero*cyanines are compared.

SEVERAL series of *mero*cyanine dyes possessing 2-alkoxy-, 2-alkylthio-, 2-(tertiary amino)-, and 2-acylamino-thiazol-5-one nuclei (I) have already been prepared and their action as optical sensitizers for photographic silver halide emulsions is known (Cook, Harris, and Shaw, *J.*, 1949, 1435; Aubert, Knott, and Williams, *J.*, 1951, 2185). One object of the present work was to prepare and examine the properties of the related 2-(secondary amino)thiazol-5-one dyes. Ghosh (*J. Indian Chem. Soc.*, 1937, **14**, 113), by refluxing *N*-thiocarbamoylglycines (II; R = *p*-Me·C_6H_4, etc.) in acetic anhydride, prepared com-

pounds which he formulated as (III; R = *p*-Me·C_6H_4, etc.). These ketomethylene heterocyclic compounds react with dye intermediates possessing electrophilic carbon atoms, to provide *mero*cyanines (I; Y = NHR). *N*-Thiocarbamoylglycines (II) are known also to form thiohydantoins (IV; R′ = H) by cyclization in mineral acid (cf. Ware, *Chem. Reviews*, 1950, **46**, 406). An examination of the products of, and the conditions



and reagents necessary for, the cyclization of (II) was therefore carried out. *N*-Thiocarbamoylglycines were prepared by condensing primary amines with the potassium salt of *N*-(ethylthio-thiocarbonyl)glycine in aqueous alcohol. Aromatic amines provided only 2-thiohydantoins, but alkaline hydrolysis of these (Ghosh, *loc. cit.*) provided *N*-(arylthiocarbamoyl)glycines.

Cyclization of N-*Thiocarbamoylglycines.*—(a) *2-Thiohydantoins. N*-(*p*-Tolylthiocarbamoyl)glycine was taken as a model compound since most of its derivatives are crystalline solids. When it was refluxed in aqueous mineral acid according to the classical method, 2-thio-3-*p*-tolylhydantoin was obtained. By heating the intermediate thiohydantoic acid in acetic anhydride on the steam-bath, the compound described by Ghosh was obtained. It corresponded, by analysis, to 1-acetyl-2-thio-3-*p*-tolylhydantoin (IV; R′ = Ac, R = *p*-Me·C_6H_4), the formation of thiohydantoins in acetic anhydride being conducive to acetylation at the 1-position (Wheeler, Nicolet, and Johnson, *Amer. Chem. J.*, 1911, **46**, 456; Komatsu, *Mem. Coll. Sci. Kyoto*, 1915, **1**, 69, etc.). Acetylation of 2-thio-3-*p*-tolylhydantoin provided the same compound, thus confirming its structure. The 1-acyl group was easily removed by mineral acid (cf. Wheeler, *et al.*, *loc. cit.*). The compounds obtained by Ghosh on refluxing his intermediates with *o*-nitrobenzaldehyde in acetic anhydride were therefore 1-acetyl-5-*o*-nitrobenzylidene-2-thiohydantoins, and reduction of these provided, not (VI), but (VII) or its acetyl derivative. A synthesis of the isomeric 2-acetylthio-4 : 5-dihydro-5-oxo-1-*p* tolylglyoxaline (V; R = *p*-Me·C_6H_4, R′ = Ac) was unsuccessfully attempted : no reaction took place between the thiohydantoin and acetyl chloride, in the presence of pyridine or potassium hydroxide.

However, *S*-methylation occurred (cf. Ware, *loc. cit.*) when methyl sulphate reacted with 2-thio-3-*p*-tolylhydantoin in alcoholic potassium hydroxide, the product being 4 : 5-dihydro-2-methylthio-5-oxo-1-*p*-tolylglyoxaline (V; R = *p*-Me·C_6H_4, R′ = Me). The isomeric 1-methyl-2-thio-3-*p*-tolylhydantoin was prepared by Delépine's method (*Bull. Soc. chim.*,

1903, **29**, 1198; Cook and Cox, *J.*, 1949, 2343) from methylaminoacetonitrile and *p*-tolyl *iso*thiocyanate. Of these substituted tolylhydantoins the only compound to form an insoluble silver salt was 2-thio-3-*p*-tolylhydantoin, since substitution in the 1-position, or at the sulphur atom prevents the formation of a free mercapto-group, and so of a silver salt.

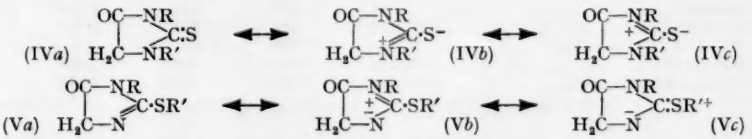
TABLE 1. *Ultra-violet absorption maxima* (mμ, *in* MeOH) *of thiohydantoins and related compounds.*

Compound	Main peak $\lambda_{max.}$	Main peak ε	Subsidiary peak $\lambda_{max.}$	Subsidiary peak ε
2-Thio-3-*p*-tolylhydantoin	262	15,400	227	9,100
1-Methyl-2-thio-3-*p*-tolylhydantoin	265	14,600	233	11,100
1-Acetyl-2-thio-3-*p*-tolylhydantoin	277	14,700	229	12,200
NN'-Diethylthiourea	265	7,300	234	6,300
4 : 5-Dihydro-2-methylthio-5-oxo-1-*p*-tolylglyoxaline	Tail absorption from 225 mμ			
NN'-Diethyl-*S*-methyl*iso*thiourea	Tail absorption from 225 mμ			

The ultra-violet absorption spectra of these compounds (Table 1) and of a group of 5 : 5-disubstituted thiohydantoins examined by Carrington (*J.*, 1947, 684) were similar. The absorption maxima were compared with those of a symmetrically substituted thiourea, and an *iso*thiourea. The two maxima, at 225—235 and 260—280 mμ, shown by thiohydantoins unsubstituted at the sulphur atom were also observed for *NN'*-diethylthiourea and are probably due to the resonance (IV*a* ⟷ *b* ⟷ *c*), greater contributions arising from (IV*b*) than from (IV*c*) because of amide resonance between the $N_{(3)}$ atom and the 4-keto-group in hydantoins. Similar peaks at 225—230 mμ and extinction coefficients have been observed by Ferm, Riebsomer, Martin, and Daub (*J. Org. Chem.*, 1953, **18**, 643) for a number of 1 : 2 : 4 : 4-tetra-alkyldihydroglyoxalines, so that this shorter-wave-length peak may be due to the (IV*b* ⟷ *c*) resonance, or to the polarizable C:N bond.

When R′ is a +*M*-group (acetyl) contributions from (IV*b*) will diminish, and a bathochromic shift of the longer-wave-length maximum is observed, *i.e.*, a reduced contribution from a polar structure increases the degeneracy in this part of the molecule. This implies that in 1-alkyl-2-thiohydantoins, the polar structures (IV*b*, *c*) predominate in the hybrid.

Neither 4 : 5-dihydro-2-methylthio-5-oxo-1-*p*-tolylglyoxaline nor *NN'*-diethyl-*S*-methyl-*iso*thiourea has an absorption peak within the range observed, showing that resonance such as (V*a* ⟷ *b* ⟷ *c*) produces only a tail absorption in the ultra-violet. That structures (V*b*, *c*) contribute little to the hybrid is borne out by the less polar nature, including lower melting points and higher solubility in non-polar solvents, of these compounds compared with their thiohydantoin isomers.



(b) *Thiazol-5-ones.* When *N*-(*p*-tolylthiocarbamoyl)glycine was treated with phosphorus tribromide in dioxan (cf. Cook *et al.* and Aubert *et al.*, *locc. cit.*) 2-*p*-toluidinothiazol-5-one hydrobromide (cf. III; R = *p*-Me·C_6H_4) was obtained, and treatment of this compound with sodium hydrogen carbonate solution provided the base as a gum. Sodium carbonate caused rearrangement of the hydrobromide to the 2-thiohydantoin. Other 2-aminothiazol-5-one hydrobromides [those of (II) in which R = alkyl, benzyl, carboxymethyl, or *cyclo*hexyl], obtained from the appropriate *N*-thiocarbamoylglycines, were more stable than the corresponding 2-(tertiary amino)-analogues but the bases were unstable and could not be purified.

2-Thiohydantoin Dyes.—The 2-thiohydantoin dyes (VIII; R′ = H) were less soluble and had higher melting points than their 1-acyl analogues (VIII; R′ = COR″), or 2-aminothiazol-5-one isomers (X). Whereas the hydantoin dyes (VIII; R′ = H) with strongly −*M* heterocycles obeyed Kundt's rule, the absorption maxima of analogous 1-acyl dyes moved hypsochromically with increasing solvent polarity (*i.e.*, the dipolar

extreme structure predominates in these dyes). Acetylation of 2-thiohydantoin dyes provided 1-acyl derivatives and sometimes paler dyes of unknown composition. Quaternization of 1-acyl dyes gave salts (IX) which did not condense further with amines or dye intermediates (cf. Jeffreys, *J.*, 1954, 389), probably because of steric effects.

Thiazol-5-one Dyes.—The 2-aminothiazol-5-one *mero*cyanines (X) isomerized, analogously to the 2-iminothiazolid-5-ones, in alcoholic alkali to 2-thiohydantoin dyes. Alkylated dyes from 2-aminothiazol-5-ones proved to be 2-iminothiazolid-5-ones (XI) by their non-identity with analogous 2-(tertiary amino)thiazol-5-ones, and by their rearrangement to 1 : 3-substituted 2-thiohydantoins (VIII; R′ = alkyl) in pyridine–carbonate solution. This alternative preparation of (XI) is an improvement on the original (Jeffreys, *loc. cit.*) as the more soluble dyes of this type are isolatable, and the yields are higher.

Acetylation of thiazol-5-one dyes produced less soluble dyes with higher melting points. These are formulated as 3-acyl-2-iminothiazolid-5-ones (XII), since alkylation occurs at the 3-position, and the acyl dyes are unlike the more soluble, lower-melting 2-(tertiary amino)thiazol-5-ones whose spatial arrangements they would resemble if acylation occurred at the 2-amino-group. Many 3-acyl dyes exhibited a reversal of Kundt's rule, and by comparison with 3-alkyl-2-thiothiazolid-5-ones (Jeffreys and Knott, *J.*, 1952, 4632) energetic degeneracy is achieved in dyes with heterocycles having weaker $-M$ effects.

For comparison with the acetylated dyes, an isomer prepared by methylation of a 2-acetamidothiazol-5 one (Aubert *et al.*, *loc. cit.*) was examined. Methylation had occurred at the 3-position, since the dye (XIII) was hydrolysed and rearranged in aqueous carbonate solution, forming (XIV), which was also synthesized unambiguously from 1-methyl-2-thiohydantoin.

The Colour of Thiazol-5-one Dyes.—The 2-aminothiazol-5-one dyes, together with the other groups of 2-substituted thiazol-5-one *mero*cyanines synthesized by Cook *et al.* and Aubert *et al.*, provide an opportunity for comparing the relative effects of 2-substituents on the colour of analogous dyes. Table 2 shows the long-wave-length absorption maxima

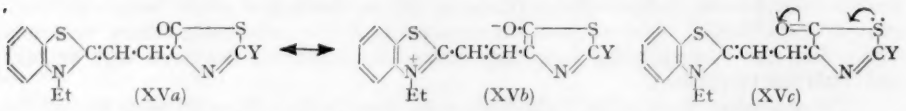
TABLE 2. *Absorption maxima* (mμ, *in* MeOH) *of dimethin*mero*cyanines possessing a 2-substituted thiazol-5-one nucleus* (I; n = 1).

(Except for Y = NHEt, the absorption maxima are taken from Aubert *et al.*, *loc. cit.*).

	Substituent Y				
Heterocycle A	NHAc	SEt	NEt_2	NHEt	OEt
Thiazolidine	480	470	469	460	452
Benzoxazoline	488	491	480	472	460
Benzothiazoline	528	527	519	508 [a]	499
Benzoselenazoline	528	528	517	508 [a]	505
Naphtho(1′ : 2′-4 : 5)thiazoline	—	548	532	520	523
1: 2-Dihydroquinoline	555	546	560	540 [b]	530
1 : 4-Dihydroquinoline	593	591	588	575 [b]	568

[a] Y = nC_8H_{17}·NH·. [b] Y = *cyclo*-C_6H_{11}·NH·.

of several series of dyes in methanol. The first three columns of the Table indicate that an increase in the $-M$ effect of the 2-substituent causes a hypsochromic shift of $\lambda_{max.}$. The reverse is the case, however, when the substituent is changed from NEt_2 to NHEt to OEt. For a typical dye, the visible absorption is due to resonance involving extreme structures (XV*a*, *b*). The majority of the dyes in Table 2, show bathochromic shifts with increased



(XV*a*) (XV*b*) (XV*c*)

solvent polarity, *i.e.*, (XV*b*) is the extreme structure of highest energy. Therefore, any change in the 2-substituent which increases the energy change (XV*a* ⟶ *b*) will cause a hypsochromic shift of $\lambda_{max.}$. As the $-M$ effect of Y increases, one would expect greater contributions to the thiocarboxylate resonance (XV*c*) from the $\cdot{}^{+}S{:}C{\cdot}O^{-}$ form, thus

increasing the energy of (XV*b*), with a consequent hypsochromic shift of $\lambda_{max.}$. Although this accounts for the shifts observed between the first three columns, no satisfactory explanation is presented for the remaining absorption changes.

Experimental

Microanalyses are partly by Mr. C. B. Dennis.

Throughout the Tables below the following solvent abbreviations are used: A = ethanol, B = benzene, D = ether, E = ethyl acetate, L = light petroleum (b. p. 60—80°), M = methanol, P = pyridine; EM–L denotes precipitation by light petroleum from ether–methanol.

N-(*Alkylthiocarbamoyl*)*glycines* (Table 3).—These were prepared according to the method of Aubert, Knott, and Williams (*loc. cit.*) for the corresponding *NN*-dialkyl compounds. Potassium hydroxide (16·8 g.) was dissolved in water (45 c.c.) and added to a solution of *N*-(ethylthio-thiocarbonyl)glycine (53·7 g.) in ethanol (90 c.c.). The primary amine was then added, and the solution was refluxed for 24 hr., concentrated, cooled in ice, and acidified with concentrated hydrochloric acid. Scratching caused crystallization, and the solution was later filtered. The product was washed with a little ice-cold water and recrystallized.

3-*Alkyl*(*or aryl*)-2-*thiohydantoins*.—*N*-Thiocarbamoylglycine (5 g.) in 2N-hydrochloric acid (25 c.c.) and ethanol (20 c.c.) was refluxed for ½ hr. On removal of the ethanol *in vacuo*, the 2-thiohydantoin crystallized, and was purified by recrystallization. The following 2-thiohydantoins were prepared: 3-methyl-, m. p. 162° (Marckwald, Neumark, and Stelzner, *Ber.*, 1891, **24**, 3285); 3-*ethyl*-, pale straw-coloured needles (from ethyl acetate–light petroleum), m. p. 144° (Found: N, 19·4. $C_5H_8ON_2S$ requires N, 19·4%); 3-carboxymethyl-, m. p. 212° (decomp.) (Johnson and Renfrew, *J. Amer. Chem. Soc.*, 1925, **47**, 240); 3-*p*-tolyl-, m. p. 228° (Johnson, Pfau, and Hodge, *ibid.*, 1912, **34**, 1044). Dyes derived from these and other 2-thiohydantoins are listed in Table 5.

Table 3. N-*Thiocarbamoylglycines* (II).

R	Appearance	M. p.	Solvent	Yield (%)	Formula	Found (%) N	Reqd. (%) N
Methyl	Prisms	171° (decomp.)	EM–L	68	$C_4H_8O_2N_2S$	18·8	18·9
Ethyl	Prisms	170 (decomp.)	EM–L	72	$C_5H_{10}O_2N_2S$	17·2	17·3
Carboxymethyl	Prisms	170 (decomp.)	EM–L	36	$C_5H_8O_4N_2S$	14·6	14·6
n-Octyl	Waxy needles	125	E–L	20	$C_{11}H_{22}O_2N_2S$	11·5	11·4
Benzyl	Microcrystalline needles	189	EM–L	60	$C_{10}H_{12}O_2N_2S$	12·8	12·5
*cyclo*Hexyl	Microcrystalline needles	156	E–L	40	$C_9H_{16}O_2N_2S$	13·0	13·0
p-Tolyl [a]	Microcrystalline needles	148 (decomp.)	Water	—	$C_{10}H_{12}O_2N_2S$	12·4	12·5
Dimethyl [b]	Microcrystalline needles	177	EM–L	50	$C_5H_{10}O_2N_2S$	17·3	17·3

[a] Ghosh, *loc. cit.*, by hydrolysis of 2-thio-3-*p*-tolylhydantoin. [b] Prepared from dimethylamine.

Table 4. 2-*Aminothiazol*-5-*one hydrobromides*.

R in (III)	M. p. (decomp.)	Formula	Found (%) N	Found (%) Br	Found (%) S	Required (%) N	Required (%) Br	Required (%) S
Methyl	170°	$C_4H_7ON_2BrS$	13·0	37·3	—	13·3	37·9	—
Ethyl [a]	203	$C_5H_9ON_2BrS$	12·3	34·6	14·2	12·4	35·6	14·2
Carboxymethyl	138	$C_5H_7O_3N_2BrS$	—	31·0	—	—	31·4	—
n-*Octyl*	192	$C_{11}H_{21}ON_2BrS$	—	25·4	—	—	25·9	—
Benzyl [b]	196	$C_{10}H_{11}ON_2BrS$	—	27·2	—	—	27·9	—
cyclo*Hexyl*	231	$C_9H_{15}ON_2BrS$	—	28·1	—	—	28·6	—
p-*Tolyl*	170	$C_{10}H_{11}ON_2BrS$	9·9	24·1	11·3	9·8	27·9	11·2

[a] Found: C, 26·8; H, 4·2. Reqd.: C, 26·7; H, 4·0%. [b] Leaflets from acetic acid.

1-*Acyl*-3-*alkyl*(*or aryl*)-2-*thiohydantoins*.—*N*-Thiocarbamoylglycine (5 g.) in the acid anhydride (30 c.c.) was heated for ½ hr. on the steam-bath, and the solvent was removed at the pump. Oils were obtained which were used without further purification in preparing the dyes. 1-*Acetyl*-2-*thio*-3-p-*tolylhydantoin* was obtained as a solid which recrystallized from

TABLE 5. mero*Cyanines* (VIII) *derived from* 1-, 3-, *and* 1 : 3-*substituted-2-thiohydantoins.*

No.	Heterocycle A	R	R′	Yield (%)	Appearance *	Solvent	M. p.	$\lambda_{max.}$ (mμ, MeOH)	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
(a) 5-(3-*Ethylbenzothiazolin*-2-*ylidene*)-2-*thiohydantoins* (A = benzothiazoline, *n* = 0).													
		Et	H	84	Yellow P	PM	248°	408	$C_{14}H_{15}ON_3S_2$	13·8	—	13·8	—
		Et	Ac	70	Lemon P	E	243	404	$C_{16}H_{17}O_2N_3S_2$	12·3	18·5	12·1	18·4
(b) 5-(3-*Ethyl*-A-*ethylidene*)-2-*thiohydantoins* (*n* = 1).													
1	Thiazolidine	Et	H	90	Yellow N	MEL	205	465	$C_{12}H_{17}ON_3S_2$	14·6	—	14·8	—
2	,,	Et	Ac	61	Orange N	MEL	179	460	$C_{14}H_{19}O_2N_3S_2$ [b]	13·0	19·8	12·9	19·7
3	,,	Et	COEt	47	Khaki N	BL	160	467	$C_{15}H_{21}O_2N_3S_2$	12·3	—	12·4	—
4	Benzoxazoline	Me	H	67	Orange N	PA	304 [a]	470	$C_{15}H_{15}O_2N_3S$	13·9	—	13·9	—
5	,,	H	Me [c]	85	Orange-red N	PM	310 [a]	480	$C_{15}H_{15}O_2N_3S$	14·0	10·6	13·9	10·6
6	,,	Me	Ac	85	Chocolate L	PBL	204	475	$C_{17}H_{17}O_3N_3S$	12·3	9·5	12·2	9·3
7	,,	Et	H	86	Orange-red P	BL	285	476	$C_{16}H_{17}O_2N_3S$	13·4	10·1	13·3	10·1
8	,,	Et	Ac	50	Orange L	BL	212	477	$C_{18}H_{19}O_3N_3S$ [d]	11·8	8·7	11·8	9·0
9	,,	Et	COEt	22	Red L, blue reflex	BL	195	481	$C_{19}H_{21}O_3N_3S$	11·2	—	11·3	—
10	,,	$CH_2{\cdot}CO_2H$	H	10	Orange	MD	279 [a]	480	$C_{16}H_{15}O_4N_3S$	12·1	—	12·2	—
11	,,	$CH_2{\cdot}CO_2H$	Ac	15	Orange-brown	AD	243	475	$C_{18}H_{17}O_5N_3S$	10·9	8·4	10·9	8·3
12	,,	n-C_8H_{17}	Ac	25	Orange	A	176	480	$C_{24}H_{31}O_3N_3S$	9·5	—	9·5	—
13	,,	$C_6H_5{\cdot}CH_2{\cdot}$	Ac	66	Orange N	BL	220	480	$C_{23}H_{21}O_3N_3S$	10·1	—	10·0	—
14	,,	p-Me·$C_6H_4{\cdot}$	H	90	Red N	PA	288 [a]	482	$C_{21}H_{19}O_2N_3S$	11·0	8·4	11·1	8·5
15	,,	p-Me·$C_6H_4{\cdot}$	Me	82	Red N	PA	243	490	$C_{22}H_{21}O_2N_3S$	10·7	8·3	10·7	8·2
16	,,	p-Me·$C_6H_4{\cdot}$	Ac	50	Orange L	PA	237	480	$C_{23}H_{21}O_3N_3S$	10·0	7·6	10·0	7·6
17	Benzothiazoline	Me	H	94	Red L	PM	317 [a]	508	$C_{15}H_{15}ON_3S_2$	13·1	—	13·2	—
18	,,	H	Me	90	Slate N	PL	284	512	$C_{15}H_{15}ON_3S_2$	13·2	20·1	13·2	20·2
19	,,	Me	Ac	70	Bronze N	PM	211	510	$C_{17}H_{17}O_2N_3S_2$	11·6	—	11·7	—
20	,,	Et	H	80	Maroon N, blue reflex	PM	308	510	$C_{16}H_{17}ON_3S_2$	12·6	—	12·7	—
21	,,	Et	Ac	71	Blue P	BL	201	512	$C_{18}H_{19}O_2N_3S_2$ [e]	11·3	16·9	11·3	17·2
22	,,	$CH_2{\cdot}CO_2H$	H	25	Maroon L	PL	280	510	$C_{16}H_{15}O_3N_3S_2$	11·7	17·8	11·6	17·7
23	,,	n-C_8H_{17}	Ac	30	Orange L	BL	180	510	$C_{24}H_{31}O_2N_3S_2$	9·1	—	9·2	—
24	,,	$C_6H_5{\cdot}CH_2{\cdot}$	Ac	55	Maroon N, bronze reflex	BL	210	510	$C_{23}H_{21}O_2N_3S_2$	9·5	14·4	9·7	14·7
25	,,	*cyclo*-$C_6H_{11}{\cdot}$	Ac	25	Crimson N	BL	221	510	$C_{22}H_{25}O_2N_3S_2$	9·9	—	9·8	—
26	Benzoselenazoline	Et	H	80	Maroon L	PM	310	505	$C_{16}H_{17}ON_3SSe$	11·1	—	11·1	—
27	,,	Et	Ac	80	Indigo L	BL	243	530	$C_{18}H_{19}O_2N_3SSe$	9·9	—	10·0	—
28	Naphth(1′ : 2′-4 : 5)oxazoline	$C_6H_5{\cdot}CH_2{\cdot}$	Ac	60	Orange L	PM	320	490	$C_{27}H_{23}O_3N_3S$	8·8	—	8·9	—
29	Naphtho(1′ : 2′-4 : 5)thiazoline	Et	H	85	Red N	B	213	530	$C_{20}H_{19}ON_3S_2$	10·9	—	11·0	—
30	,,	Et	Ac	57	Maroon N	BL	210	530	$C_{22}H_{21}O_2N_3S_2$	9·7	—	9·9	—
31	1 : 2-Dihydroquinoline	Et	H	81	Blue N	PM	278	540	$C_{18}H_{19}ON_3S$	12·9	—	12·9	—
32	,,	Et	Ac	60	Indigo	PM	207	535	$C_{20}H_{21}O_2N_3S$	11·5	—	11·4	—
33	1 : 4-Dihydroquinoline	Et	H	65	Emerald N	PM	237	574 [f]	$C_{18}H_{19}ON_3S$	9·8	—	9·9	—
34	,,	Et	Ac	16	Dark green N	BL	184	610	$C_{20}H_{21}O_2N_3S$	11·5	—	11·4	—
35	4 : 5-Diphenyloxazoline	Et	H	76	Brick-red P	PM	283	500	$C_{24}H_{23}O_2N_3S$	10·1	—	10·1	—
36	,,	Et	Ac	14	Maroon	BL	200	500	$C_{26}H_{25}O_3N_3S$	9·0	—	9·1	—
37	4 : 5-Diphenylthiazoline	Et	H	86	Emerald L	PM	283	540	$C_{24}H_{23}ON_3S_2$	9·8	—	9·7	—
38	,,	Et	Ac	50	Brown L	BL	210	540	$C_{26}H_{25}O_2N_3S_2$	8·9	13·3	8·8	13·5
(c) 5-[4-(3-*Ethyl*-A)-*but*-2-*en*-1-*ylidene*]-2-*thiohydantoin* (*n* = 2).													
39	Benzothiazoline	Et	H	20	Blue N	BL	254	550	$C_{18}H_{19}ON_3S_2$	11·6	—	11·8	—
40	,,	Et	Ac	15	Indigo N	BL	155	560	$C_{20}H_{21}O_2N_3S_2$	10·8	—	10·5	—

[a] With decomp. [b] Found: C, 52·0; H, 5·9. Reqd.: C, 51·7; H, 5·9%. [c] From 1-methyl-2-thiohydantoin (Komatsu, *loc. cit.*). [d] Found: C, 61·0; H, 5·2. Reqd.: C, 60·5; H, 5·3%. [e] Found: C, 58·1; H, 5·2. Reqd.: C, 57·9; H, 5·1%. [f] Also (613). The following list is of dyes and absorption maxima (mμ) in benzene, and in aqueous methanol (1 : 2). No. 7, 460, 485; No. 8, 474, 490; No. 20, 490, 520; No. 21, 505, 517; No. 33, 550, (580), 617; No. 34, 570, 585; No. 35, 491, 503; No. 36, 503, 480. * L = leaflets, N = needles, P = prisms.

ethanol as cream leaflets (4·4 g.), m. p. 157° (Found : N, 11·2; S, 12·9. $C_{12}H_{12}O_2N_2S$ requires N, 11·3; S, 12·9%) (cf. Ghosh, *loc. cit.*).

Acetylation of 2-*Thio*-3-p-*tolylhydantoin*.—To a solution of 2-thio-3-*p*-tolylhydantoin (4·1 g.) and potassium hydroxide (1·1 g.) in ethanol (30 c.c.) and water (5 c.c.), cooled in ice, acetyl chloride (1·6 g.) was added. After 1 hr., water was added, and the precipitate filtered off. It was identical with the starting material, as was also the case when the reaction was carried out in dioxan, with pyridine replacing potassium hydroxide.

2-Thio-3-*p*-tolylhydantoin (2·1 g.) in acetic anhydride (30 c.c.), with and without sodium acetate (2·1 g.), was refluxed for 10 min. The solvent was removed at the pump, and the product washed with water. It was identical with 1-acetyl-2-thio-3-*p*-tolylhydantoin, described above.

Hydrolysis of 1-*Acetyl*-3-*methyl*-2-*thiohydantoin*.—1-Acetyl-3-methyl-2-thiohydantoin (1·7 g.), ethanol (4 c.c.), and 2N-hydrochloric acid (6 c.c.) were heated for 10 min. on the steam-bath. The ethanol was removed at the pump, and the precipitate recrystallized from ethyl acetate as needles, m. p. 162°. It was identical with 3-methyl-2-thiohydantoin.

4 : 5-*Dihydro*-2-*methylthio*-5-*oxo*-1-p-*tolylglyoxaline* (V; R = *p*-Me·C_6H_4, R′ = Me).—To 2-thio-3-*p*-tolylhydantoin (4·1 g.) and potassium hydroxide (1·1 g.) in ethanol (30 c.c.) and water (5 c.c.), methyl sulphate (2·52 g.) was added drop by drop, the solution being cooled in ice. After ½ hr. water (150 c.c.) was added, and the precipitate filtered off. It recrystallized from benzene–light petroleum as a cream-coloured powder (3·9 g.), shrinking at 93°, m. p. 113° (Found : N, 12·6; S, 14·5. $C_{11}H_{12}ON_2S$ requires N, 12·7; S, 14·6%).

1-*Methyl*-2-*thio*-3-p-*tolylhydantoin*.—Methylaminoacetonitrile (2·5 g.) in ether (10 c.c.) was added to cooled, stirred *p*-tolyl *iso*thiocyanate (5·3 g.) in ether (10 c.c.) under nitrogen. After 1 hr., the oil which had formed was separated and refluxed for 1 hr. with 2N-hydrochloric acid (50 c.c.). The product was filtered off (4·6 g.) and recrystallized from *iso*propanol as cream leaflets, m. p. 149° (Found : N, 12·8; S, 14·6. $C_{11}H_{12}ON_2S$ requires N, 12·7; S, 14·6%).

2-(*Secondary Amino*)*thiazol*-5-*one Hydrobromides*.—The *N*-thiocarbamoylglycine (0·01 mol.) was suspended in dioxan (20—40 c.c.), and phosphorus tribromide (0·01 mol.) was added slowly with cooling and stirring. On addition of ether (20—40 c.c.) the required *hydrobromide* (see Table 4) separated as a white powder in 90—100% yield. It was washed well with ether, and dried in a vacuum desiccator. 2-Dimethylaminothiazol-5-one hydrobromide was obtained as a deliquescent solid by a similar procedure (Aubert, Knott, and Williams, *loc. cit.*). Dyes derived from thiazol-5-one intermediates are listed in Table 7.

Dye Syntheses.—mero*Cyanines* were prepared by heating the appropriate keto-methylene compound (0·01 mol.) with a 2-alkylthiobenzothiazole quaternary salt (0·01 mol.) and triethylamine (0·01 mol.) in ethanol on the steam-bath for 15 min. *Dimethin*- and *tetramethin*-mero*cyanines* were prepared similarly, by employing 2-2′-acetanilidovinyl and 2-(4-acetanilidobuta-1 : 3-dienyl)heterocyclic quaternary salts in place of the 2-alkylthio-intermediate, with a reaction time of 5—10 min. With the hydrobromides of keto-methylene compounds, 0·02 mol. of triethylamine was used.

4-(3-*Ethylbenzoxazolin*-2-*ylidene-ethylidene*)-4 : 5-*dihydro*-2-*methylthio*-5-*oxo*-1-p-*tolylglyoxaline* [Derived from (V; R = *p*-Me·C_6H_4, R′ = Me)].—4 : 5-Dihydro-2-methylthio-5-oxo-1-*p*-tolylglyoxaline (1·1 g.) and 2-2′-acetanilidovinylbenzoxazole ethiodide (2·2 g.) with triethylamine (0·7 c.c.) in ethanol (10 c.c.) were refluxed for 10 min., chilled, and filtered. The *dye* recrystallized from benzene–light petroleum as an orange powder (0·5 g.), m. p. 194° (Found : N, 10·7; S, 8·2. $C_{22}H_{21}O_2N_3S$ requires N, 10·7; S, 8·2%). It had $\lambda_{max.}$ 473 mμ (ε 7·7 × 10^4 in MeOH).

TABLE 6. *Acetylation of* 2-*thiohydantoin dyes*.

Dye acetd., no.	Product, no.[a]	Appearance (From BL)	M. p.	$\lambda_{max.}$ (mμ, MeOH)	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
7	8	As for Dye 8, Table 5							
14	Unknown	Orange [b]	197°	460	$C_{23}H_{21}O_3N_3S$	10·1	7·6	10·0	7·6
20	21	As for Dye 21, Table 5							
35	Unknown	Yellow	194	454	$C_{26}H_{25}O_3N_3S$	9·1	6·9	9·1	7·0
37	Unknown	Orange [b]	240	488	$C_{26}H_{25}O_2N_3S_2$	7·5	12·5	8·8	13·5

[a] Yields : No. 8, 80%; No. 21, 68%. [b] Leaflets.

Acetylation of 2-*Thiohydantoin Dyes* (Table 6).—The appropriate dimethin*mero*cyanine (0·5 g.) was refluxed for 15 min. with sodium acetate (0·5 g.) in acetic anhydride (15 c.c.). If the product did not crystallize on cooling, the solution was poured into water and shaken for ½ hr. The *dye* was filtered off, washed, and recrystallized.

TABLE 7. mero*Cyanines derived from 2-aminothiazol-5-ones* (X).

No.	Heterocycle A	R	Yield, %	Appearance *	Solvent	M. p.	$\lambda_{max.}$ (mμ, MeOH)	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
(a) 2-(*Secondary amino*)-4-(3-*ethylbenzothiazolin*-2-*ylidene*)*thiazol*-5-*ones* (A = benzothiazoline, n = 0).												
41	—	Et	59	Yellow P	BL	170°	414	$C_{14}H_{15}ON_3S_2$ [a]	13·8	21·1	13·8	21·0
42	—	n-C_8H_{17}	20	Yellow N	BL	180	413	$C_{20}H_{27}ON_3S_2$	—	16·5	—	16·5
(b) 2-(*Secondary amino*)-4-(3-*ethyl*-A-*ethylidene*)-*thiazol*-5-*ones* (n = 1).												
43	Thiazolidine	Et	30	Red N	BL	184	460	$C_{12}H_{17}ON_3S_2$	14·8	—	14·8	—
44	,,	*cyclo*-C_6H_{11}	80	Orange N	M	62	462	$C_{16}H_{23}ON_3S_2$	12·6	—	12·5	—
45	Benzoxazoline	Me	85	Orange L	BL	207	472	$C_{15}H_{15}O_2N_3S$	13·8	—	13·9	—
46	,,	Et	94	Maroon, P, purple reflex	BL	162	472	$C_{16}H_{17}O_2N_3S$ [b]	13·1	10·2	13·3	10·1
47	,,	CH_2CO_2H	32	Maroon P	PM	195 †	470	$C_{16}H_{15}O_4N_3S$	12·2	—	12·2	—
48	,,	*cyclo*-C_6H_{11}	68	Orange P	M	158	470	$C_{20}H_{23}O_2N_3S$	11·5	—	11·4	—
49	,,	*p*-Me·C_6H_4·	58	Magenta N	M	215	490	$C_{21}H_{19}O_2N_3S$	11·1	8·5	11·1	8·5
50	Benzothiazoline	Me	88	Maroon N	BL	199	497	$C_{15}H_{15}ON_3S_2$	13·2	—	13·2	—
51	,,	Et	60	Maroon N	BL	105	497	$C_{16}H_{17}ON_3S_2$	12·7	19·1	12·7	19·3
52	,,	n-C_8H_{17}	16	Red	BL	192	498	$C_{22}H_{29}ON_3S_2$	10·0	—	10·1	—
53	,,	C_6H_5·CH_2·	35	Purple P	BL	158	494	$C_{21}H_{19}ON_3S_2$ [c]	10·5	16·2	10·7	16·3
54	,,	*p*-Me·C_6H_4·	52	Slate N	M	190	510	$C_{21}H_{19}ON_3S_2$	10·7	—	10·7	—
55	Benzoselenazoline	n-C_8H_{17}	15	Maroon	BL	217	508	$C_{22}H_{29}ON_2SSe$	9·0	—	9·1	—
56	Naphtho(1′ : 2′-4 : 5)thiazoline	Et	25	Chocolate	BL	186	520	$C_{20}H_{19}ON_3S_2$	10·9	—	11·0	—
57	1 : 2-Dihydroquinoline	*cyclo*-C_6H_{11}	10	Indigo	M	280	540	$C_{22}H_{25}ON_3S$	11·0	—	11·1	—
58	1 : 4-Dihydroquinoline	*cyclo*-C_6H_{11}	60	Green L	M	156	575	$C_{22}H_{25}ON_3S$	11·1	—	11·1	—
59	4 : 5-Diphenyloxazoline	Et	52	Orange-brown N	BL	225	506	$C_{24}H_{23}O_2N_3S$	10·2	7·9	10·1	7·7
(c) *Other* 2-*amino*-4-(3-*ethyl*-A-*ethylidene*)*thiazol*-5-*ones*.												
60	Benzoxazoline	Me_2 [d]	63	Orange-red N	BL	208	480	$C_{16}H_{17}O_2N_3S$	13·2	—	13·3	—
61	Benzothiazoline	Me_2 [d]	75	Green N	BL	217	505	$C_{16}H_{17}ON_3S_2$	12·9	—	12·7	—

[a] Found: C, 55·3; H, 5·0. Reqd.: C, 55·1; H, 4·9%. [b] Found: C, 61·1; H, 5·4. Reqd. C, 61·0; H, 5·4%. [c] Found: C, 64·1; H, 5·0. Reqd.: C, 64·1; H, 4·8%. [d] 2-(Tertiary amino) thiazol-5-ones prepared according to Aubert *et al.*, *loc. cit.* The following list is of dyes and absorption maxima (mμ) in benzene, and in aqueous methanol (1 : 2). No. 46, 469, 486; No. 51, 497, 512; No. 58, 557, 605; No. 59, 501, 509.

* L = leaflets, N = needles, P = prisms. † With decomp.

TABLE 8. *Acylation of* 2-(*secondary amino*)*thiazol*-5-*one* mero*cyanines*.

No.	Heterocycle A	R	R′	Yield (%)	Appearance *	Solvent	M. p.	$\lambda_{max.}$ (mμ, MeOH)	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
(a) 3-*Acetyl*-4-(3-*ethylbenzothiazoline*-2-*ylidene*)-2-*ethyliminothiazolid*-5-*one* (XII; A = benzothiazoline, n = 0).													
62	—	Et	Me	96	Lemon N	PM	211°	409(393)	$C_{16}H_{17}O_2N_3S_2$	12·0	—	12·1	—
(b) 3-*Acyl*-4-(3-*ethyl*-A-*ethylidene*)-2-*iminothiazolid*-5-*ones* (XII; n = 1).													
63	Thiazolidine	*cyclo*-C_6H_{11}	Me	40	Steel blue P	M	168	459	$C_{18}H_{25}O_2N_3S_2$ [a]	11·0	16·8	11·1	16·9
64	Benzoxazoline	Me	Me	62	Orange	PM	250	493	$C_{17}H_{17}O_3N_3S$	12·2	—	12·2	—
65	,,	Et	Me	77	Orange L	PA	239	483	$C_{18}H_{19}O_3N_3S$	11·9	—	11·8	—
66	,,	*p*-Me·C_6H_4·	Me	81	Orange N	M	215	491	$C_{23}H_{21}O_3N_3S$	10·0	7·8	10·0	7·6
67	,,	*cyclo*-C_6H_{11}	Et	43	Orange-brown	A	200	482	$C_{23}H_{27}O_3N_3S$	9·9	7·4	9·9	7·5
68	Benzothiazoline	Me	Me	66	Gold L	P	282	526	$C_{17}H_{17}O_2N_3S_2$	—	17·6	—	17·8
69	,,	C_6H_5·CH_2·	Et	88	Blue P	BL	195	505	$C_{24}H_{23}O_2N_3S_2$	9·3	14·2	9·4	14·2
70	Naphtho(1′ : 2′-4 : 5)thiazoline	Et	Me	70	Bronze N	PM	233	540	$C_{22}H_{21}O_2N_3S_2$	9·9	—	9·9	—
71	1 : 4-Dihydroquinoline	*cyclo*-C_6H_{11}	Me	50	Dull green	EL	127	580	$C_{24}H_{27}O_2N_3S$	9·9	—	10·0	—
72	4 : 5-Diphenyloxazoline	Et	Me	57	Red N	BAL	240	485	$C_{26}H_{25}O_3N_3S$	8·8	6·7	9·1	7·0

[a] Found: C, 56·9; H, 6·7. Reqd.: C, 57·0; H, 6·6%. The following list is of dyes and absorption maxima (mμ) in benzene, and aqueous methanol (1 : 2) No. 67, 484, 482; No. 69, 519, 490; No. 71, 584, 582; No. 72, 495, 480. * L = leaflets, N = needles, P = prisms.

3-Acetyl-1-benzyl-4-(3-ethylbenzoxazolin-2-ylidene-ethylidene)-4 : 5-dihydro-2-methylthio-5-oxoglyoxalinium Toluene-p-sulphonate (IX; R = benzyl, R′ = Me, Z = toluene-*p*-sulphonate).—Dye 13, Table 5 (1·4 g.), and methyl toluene-*p*-sulphonate (0·7 g.) were heated at 160° for 3 hr. A glass was obtained which recrystallized from ethanol–ether as orange needles, m. p. 189° (Found: C, 61·2; H, 5·2; N, 7·2; S, 10·6. $C_{31}H_{31}O_6N_3S_2$ requires C, 61·5; H, 5·1; N, 6·9; S, 10·6%). It was insoluble in benzene and only slightly soluble in hot water.

Alkylation Experiments.—*4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-3-methyl-2-methyliminothiazolid-5-one.* 4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-2-methylaminothiazol-5-one (dye 50, Table 7) (1·6 g.) and methyl toluene-*p*-sulphonate (0·95 g.) were heated at 140° for ½ hr. The cooled mass was dissolved in ethanol (25 c.c.) and poured into an excess of aqueous sodium carbonate. The *dye* which was precipitated recrystallized from benzene–light petroleum as maroon needles, m. p. 181° (Found: C, 58·2; H, 5·2; N, 12·7; S, 19·6. $C_{16}H_{17}ON_3S_2$ requires C, 58·0; H, 5·1; N, 12·7; S, 19·3%). It had $\lambda_{max.}$ 510 mμ in MeOH.

In a similar manner the following were prepared: *4-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-ethylimino-3-methylthiazolid-5-one*, maroon needles, m. p. 185° (from benzene–light petroleum), $\lambda_{max.}$ 517 mμ in MeOH (Found: N, 12·3; S, 18·8. $C_{17}H_{19}ON_3S_2$ requires N, 12·2; S, 18·6%); *3-ethyl-4-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-ethyliminothiazolid-5-one*, magenta needles, m. p. 184° (from benzene–light petroleum), $\lambda_{max.}$ 520 mμ in MeOH (Found: N, 11·6; S, 17·8. $C_{18}H_{21}ON_3S_2$ requires N, 11·7; S, 17·8%).

Rearrangement of 2-Aminothiazol-5-one and 2-Iminothiazolid-5-one mero*Cyanines.*—4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-2-methylaminothiazol-5-one (dye 50, Table 7) (0·5 g.) and potassium hydroxide (0·5 g.) in ethanol (40 c.c.) and pyridine (30 c.c.) were heated on the steam-bath for 3 hr. The solution was poured into water and the dye was filtered off. It recrystallized from pyridine–ethanol as red leaflets, m. p. 317° (decomp.), and was identical with an authentic sample of 5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-3-methyl-2-thiohydantoin (dye 17, Table 5).

In the same way 4-(3-ethylbenzoxazolin-2-ylidene-ethylidene)-2-*p*-toluidinothiazol-5-one (dye 49, Table 7) in alcoholic potassium hydroxide, heated on the steam-bath for ½ hr., isomerized to 5-(3-ethylbenzoxazolin-2-ylidene-ethylidene)-2-thio-3-*p*-tolylhydantoin (dye 14, Table 5), identical with an authentic specimen.

4-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-3-methyl-2-methyliminothiazolid-5-one (0·2 g.), dissolved in pyridine (10 c.c.) with aqueous sodium carbonate (2N; 5 c.c.), was heated for 1 hr. on the steam-bath. The product was precipitated with water, washed with ethanol, and recrystallized from pyridine–methanol as maroon needles, m. p. 235°. It was identical with an authentic sample of 5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-1 : 3-dimethyl-2-thiohydantoin (Jeffreys, *loc. cit.*; Table 1, dye 4).

In the same way, 4-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-ethylimino-3-methylthiazolid-5-one isomerized to 3-ethyl-5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-1-methyl-2-thiohydantoin (Jeffreys, *loc. cit.*; Table 1, dye 9).

Acylation of 2-(Secondary Amino)thiazol-5-one Dyes (Table 8).—The appropriate *mero*cyanine (0·5 g.) and sodium acetate (0·5 g.) in acetic anhydride (15 c.c.) were refluxed for 15 min. If the product did not crystallize on cooling, the solution was poured into water and shaken for ½ hr. The dye was filtered off, washed, and recrystallized. Propionylation was carried out similarly in propionic anhydride, but without sodium propionate.

Hydrolysis of a 3-Acetylthiazolid-5-one mero*Cyanine.*—3-Acetyl-4-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-methyliminothiazolid-5-one (Table 8, dye 68) (0·3 g.) and potassium hydroxide (0·3 g.) in pyridine (30 c.c.) and water (5 c.c.) were heated for 1 hr. on the steam-bath. The solution was neutralized with concentrated hydrochloric acid and poured into water. The dye which was precipitated recrystallized from benzene–light petroleum as maroon leaflets, m. p. 199°, and was identical with an authentic sample of 4-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-methylaminothiazol-5-one (Table 7, dye 50).

2-Acetimido-4-(3-ethylbenzoxazolin-2-ylidene-ethylidene)-3-methylthiazolid-5-one (XIII).—2-Acetamido-4-(3-ethylbenzoxazolin-2-ylidene-ethylidene)thiazol-5-one (Aubert *et al.*, *loc. cit.*) (1·6 g.) and methyl toluene-*p*-sulphonate (1·0 g.) were heated for 3 hr. at 140°. The mixture fused and solidified. It was dissolved in ethanol and poured into aqueous sodium carbonate. The dye was filtered off and recrystallized from benzene–light petroleum as red-bronze leaflets (1·2 g.), m. p. 233° (Found: N, 12·3; S, 9·3. $C_{17}H_{17}O_3N_3S$ requires N, 12·2; S, 9·3%). It had $\lambda_{max.}$ 504 mμ in MeOH.

This dye (0·3 g.) in ethanol (15 c.c.) with aqueous sodium carbonate (N; 10 c.c.) was refluxed for 2 hr. The solution was cooled and filtered, and the product recrystallized from pyridine–

methanol as red needles, m. p. 310°. It was identical with 5-(3-ethylbenzoxazolin-2-ylidene-ethylidene)-1-methyl-2-thiohydantoin (XIV; Table 5, dye 5).

The author is indebted to Dr. E. B. Knott for helpful discussion and to Mr. A. Pilbeam for the preparation of some intermediates.

RESEARCH LABORATORIES, KODAK LTD., WEALDSTONE,
HARROW, MIDDLESEX.

[*Received, January 27th,* 1954.]

Steroids and Walden Inversion. Part XII. The Epimeric 3-Cholesterylacetic and 3-Cholestanylacetic Acids.*

By C. W. SHOPPEE and R. J. STEPHENSON.

[Reprint Order No. 5114.]

The epimeric 3-cholesterylacetic acids have been prepared and the configuration of 3α-cholesterylacetic acid has been established by partial synthesis from 6-oxo- and 6β-hydroxy-3β-cholestanyl toluene-*p*-sulphonate by condensation with diethyl sodiomalonate.

3β-Cholesterylacetic acid has been degraded by the Wieland–Barbier procedure to cholest-5-ene-3β-carboxylic acid and has been regenerated from this acid by the Arndt–Eistert reaction.

By catalytic hydrogenation 3β-cholesterylacetic acid gives 3β-cholestanylacetic acid, but 3α-cholesterylacetic acid gives 3α-coprostanylacetic acid. 3α-Cholestanylacetic acid has been prepared by an unambiguous partial synthesis from 3β-cholestanyl toluene-*p*-sulphonate and diethyl sodiomalonate, which establishes its configuration, and, by exclusion, that of 3β-cholestanylacetic acid.

Wieland–Barbier degradation of 3β-cholestanylacetic acid gives cholestane-3β-carboxylic acid, and 3α-cholestanylacetic acid similarly affords cholestane-3α-carboxylic acid.

By condensation of cholesteryl toluene-*p*-sulphonate with diethyl sodiomalonate in xylene Kaiser and Svarz (*J. Amer. Chem. Soc.*, 1945, **67**, 1309) obtained a mixture of malonic esters, converted by alkaline hydrolysis into a mixture of malonic acids. They isolated an " acid A," m. p. 206° (decomp.), $[\alpha]_D$ −22·5°, characterised by a dimethyl ester, double m. p. 88°/106°, $[\alpha]_D$ −28°, reacting with 1 mol. of perbenzoic acid; they regarded this as a 3-cholesterylmalonic acid. Decarboxylation of " acid A " at the m. p. failed to yield any crystalline material, but " crude acid A," m. p. *ca.* 180°, gave a ~10% yield of a 3-cholesterylacetic acid, m. p. 213°, characterised by a methyl ester, m. p. 108°. They also isolated an impure amorphous " acid B," $[\alpha]_D$ +39·5°, giving an oily methyl ester reacting with only 0·31 mol. of perbenzoic acid, which by decarboxylation at 140° furnished <5% of the 3-cholesterylacetic acid, m. p. 213°. On account of the positive value of the specific rotation and the absence of a double bond, they regarded the main component of " acid B " as 3 : 5-*cyclo*cholestan-6β-ylmalonic acid, which they subsequently isolated, m. p. 174° (decomp.), $[\alpha]_D$ +65°, characterised as the dimethyl ester, m. p. 71°, $[\alpha]_D$ +58° (*ibid.*, 1947, **69**, 847), and decarboxylated to 3 : 5-*cyclo*cholestan-6β-ylacetic acid, m. p. 112°, $[\alpha]_D$ +32° (*ibid.*, 1949, **71**, 517).

Recently, a product fortuitously but correctly (see below) described as 3β-cholesterylmalonic acid {m. p. 203°, $[\alpha]_D$ −30·5° (methyl ester, m. p. 84—89°)} was obtained by Ralls (*ibid.*, 1953, **75**, 2123); cholesta-3 : 5-dien-7-one by addition of diethyl sodiomalonate gave diethyl 7-oxo-3β-cholesterylmalonate, from which the 7-oxygen function was removed by the thiol–Raney nickel procedure; there seems little doubt that this preparation is identical with the " acid A " of Kaiser and Svarz.

Similarly, a product incorrectly described as 3β-cholesterylacetic acid (m. p. 210—220°; methyl ester, m. p. 106—108°) has been obtained by Tsuda and Hayatsu (*J. Pharm. Soc. Japan*, 1952, **72**, 1303); cholesteryl toluene-*p*-sulphonate by treatment with hot

* Part XI, *J.*, 1953, 1709.

γ-picoline gave a 3-cholesteryl-4'-pyridylmethane (also prepared by condensation of 4-pyridylmethyl-lithium and cholesteryl bromide), which as the methiodide was oxidised with potassium ferricyanide to the pyridone, further oxidised by chromium trioxide to a 3-cholesterylacetic acid, which was shown by direct comparison, as the methyl ester, to be identical with the decarboxylation product of Kaiser and Svarz's " crude acid A."

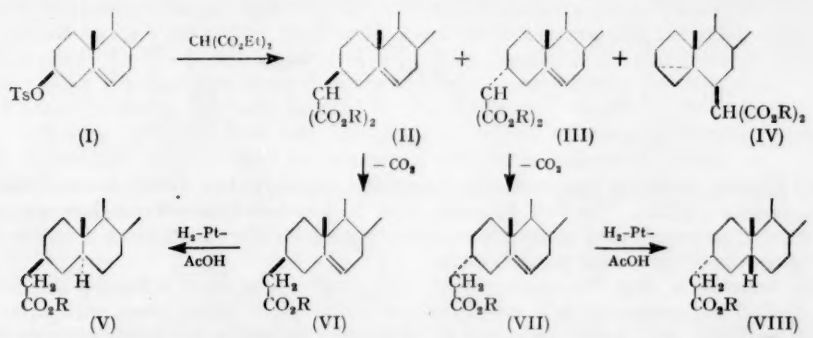
Baker and Petersen (*J. Amer. Chem. Soc.*, 1951, **73**, 4080) extended the $C_{(3)}$-side chain of the cholest-5-ene-3-carboxylic acid (Marker's acid), obtained from cholesteryl chloride by treatment with magnesium and carbon dioxide (Marker, Oakwood, and Crookes, *ibid.*, 1936, **58**, 481), by the reaction sequence:

$$-CO_2H \xrightarrow{LiAlH_4} -CH_2\cdot OH \xrightarrow{TsCl\text{–}Py} -CH_2\cdot OTs \xrightarrow{NaI} -CH_2I \xrightarrow{Mg\text{–}CO_2} -CH_2\cdot CO_2H$$

(Ts = *p*-$C_6H_4Me\cdot SO_2$; Py = C_5H_5N),

which preserves the original configuration at $C_{(3)}$, and obtained another 3-cholesterylacetic acid, m. p. 175°, $[\alpha]_D$ −31°, giving a methyl ester, m. p. 79°, $[\alpha]_D$ −32°. They attributed the 3β-configuration to the acid, m. p. 213°, of Kaiser and Svarz, and assigned the 3α-configuration to their isomeric acid, m. p. 175°, and so by implication to Marker's acid; they supported these configurational assignments by reference to Squire's work (*ibid.*, 1951, **73**, 5768), which appeared " clearly to demonstrate that opposite configurations are obtained by carbonating [3β-]cholestanyl or cholesteryl Grignard reagents." As will be shown later (Part XIII, in the press), this " demonstration " is devoid of experimental foundation.

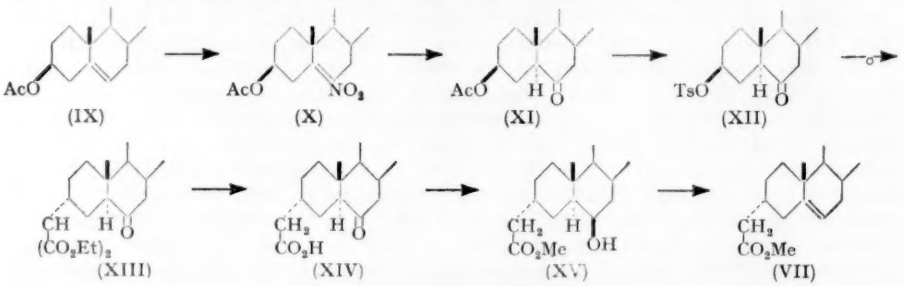
We have repeated Kaiser and Svarz's work; we find that these workers isolated a minor reaction product (" acid A ") but failed to obtain the major unrearranged product. Condensation of cholesteryl toluene-*p*-sulphonate (I) with diethyl sodiomalonate and alkaline hydrolysis of the reaction product gives a mixture containing much 3β-cholesterylmalonic acid (" acid A ") (II; R = H) and a little 3α-cholesterylmalonic acid (III; R = H). Repeated fractional crystallisation gave a product, m. p. 205° (decomp.), $[\alpha]_D$ −31°, consisting essentially of the 3β-malonic acid (II; R = H), although still slightly contaminated with the epimeric 3α-acid (III; R = H), and giving by decarboxylation at 205°/0·5 mm. an 80% yield of 3β-cholesterylacetic acid (VI; R = H), isolated chromatographically as the methyl ester, identical with Baker and Petersen's acid, and converted by catalytic hydrogenation into 3β-cholestanylacetic acid (V; R = H). The small proportion of 3α-cholesterylmalonic acid (III; R = H) also underwent decarboxylation, to yield 3α-cholesterylacetic acid (VII; R = H), isolated by repeated fractional crystallisation as the methyl ester and identical with Kaiser and Svarz's acid. Catalytic hydrogenation of 3α-cholesterylacetic acid (VII; R = H) gave an acid which we regard as 3α-coprostanylacetic acid (VIII), the formation of which appears to furnish a further example of the influence of a 3α-substituent on the stereochemical course of hydrogenation of an appropriately located double bond (Lewis and Shoppee, *Chem. and Ind.*, 1953, 897).



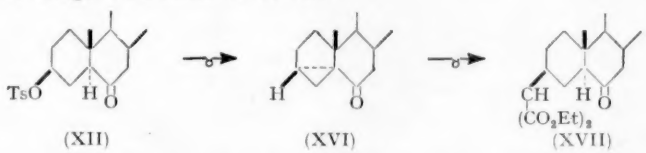
3α-Cholesterylacetic acid is much less soluble than the 3β-epimeride in acetone, and is readily separated from mixtures with it by fractional crystallisation from acetone. It is because of this marked difference that Kaiser and Svarz isolated only some 10% of the

minor reaction product, 3α-cholesterylacetic acid (VII), after decarboxylation of their " crude acid A."

The configuration of 3α-cholesterylacetic acid (VII; R = H) follows from the following partial syntheses. Cholesteryl acetate (IX) by nitration yielded 6-nitrocholesteryl acetate (X), transformed by treatment with zinc–acetic acid into 6-oxocholestan-3β-yl acetate (XI); this which was converted by alkaline hydrolysis and re-esterification into 6-oxocholestan-3β-yl toluene-*p*-sulphonate (XII). Toluene-*p*-sulphonates of saturated steroids are known to undergo alkyl–oxygen fission, Ts-O—R, so that substitution takes place with inversion of configuration (Plattner and Fürst, *Helv. Chim. Acta*, 1943, **26**, 2266; Prelog and Szpilfogel, *ibid.*, 1944, **27**, 390; Plattner *et al.*, *ibid.*, 1948, **31**, 1457, footnote 1; Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937; Elks and Shoppee, *J.*, 1953, 241); condensation of the toluene-*p*-sulphonate (XII) with diethyl sodiomalonate gave diethyl 6-oxocholestan-3α-ylmalonate (XIII), converted by alkaline hydrolysis into the related malonic acid, which was decarboxylated at 170°/0·5 mm. to 6-oxocholestan-3α-ylacetic acid (XIV). This acid was esterified with diazomethane, and the keto-ester was reduced with sodium borohydride * to methyl 6β-hydroxycholestan-3α-ylacetate (XV), which by ionic dehydration with phosphorus oxychloride and pyridine [6β-OH(polar) : 5α-H(polar) : *trans*] was smoothly converted into methyl 3α-cholesterylacetate (VII; R = Me).



The neutral fraction isolated from the reaction of 6-oxocholestan-3β-yl toluene-*p*-sulphonate (XII) with the diethyl malonate anion $^-CHR_2$ consisted mainly of 3 : 5-*cyclo*cholestan-6-one (XVI) accompanied by a little of a ketonic substance, m. p. 185°, which we have not yet identified. Since 3 : 5-*cyclo*cholestan-6-one (XVI) is readily formed by elimination (*E*2) from 6-oxocholestan-3β-yl toluene-*p*-sulphonate (XII), by treatment with anions ^-OR (cf. Shoppee and Summers, *J.*, 1952, 3361), an alternative pathway in which the 3 : 5-*cyclo*-ketone simulates the properties of an αβ-unsaturated ketone (cf. Linstead *et al.*, *J.*, 1952, 3610; 1953, 1799) and undergoes a Michael reaction with *trans*-addition to the bridge bond could be written :

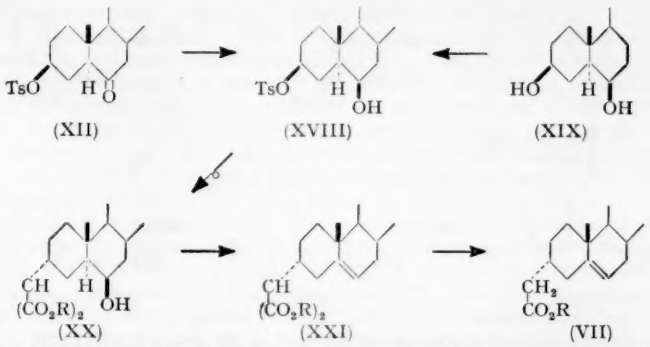


Such a process, involving two successive inversions, would lead to diethyl 6-oxocholestan-3β-ylmalonate (XVII). We find, however, that 3 : 5-*cyclo*cholestan-6-one does not react with diethyl sodiomalonate under the conditions used for the substitution reaction with 6-oxocholestan-3β-yl toluene-*p*-sulphonate.

Our conclusion that the condensation of 6-oxocholestan-3β-yl toluene-*p*-sulphonate with diethyl sodiomalonate is a substitution reaction [S_N2] taking place with inversion (XII → XIII) has been confirmed as follows. Reduction of 6-oxocholestan-3β-yl

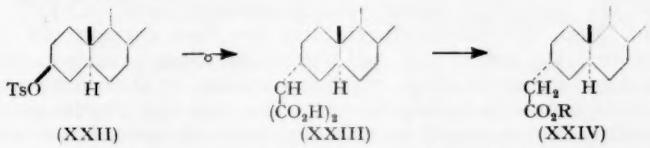
* Use of lithium aluminium hydride furnished the same 2-(6β-hydroxycholestan-3α-yl)ethanol, characterised as the diacetate, as was obtained by reduction of the 6β-hydroxy-ester (XV) with lithium aluminium hydride.

toluene-*p*-sulphonate (XII) with sodium borohydride occurs with preservation of the toluene-*p*-sulphonyloxy-group, to yield 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (XVIII), identical with a specimen previously prepared from cholestane-3β : 6β-diol (XIX) by treatment with 1 mol. of toluene-*p*-sulphonyl chloride in pyridine (Shoppee and Summers, unpublished work; cf. Reich and Lardon, *Helv. Chim. Acta*, **1946**, **29**, 761). Condensation with diethyl sodiomalonate gave, after alkaline hydrolysis, 6β-hydroxycholestane-3α-ylmalonic acid (XX; R = H), dehydrated as the dimethyl ester to dimethyl 3α-cholesterylmalonate (XXI; R = Me). Alkaline hydrolysis furnished 3α-cholesterylmalonic acid (XXI; R = H), which by decarboxylation afforded 3α-cholesterylacetic acid (VII; R = H).



(XII) (XVIII) (XIX) (XX) (XXI) (VII)

Finally, we have obtained 3α-cholestanylacetic acid (XXIV; R = H) by the following unambiguous partial synthesis. 3β-Cholestanyl toluene-*p*-sulphonate (XXII) by condensation with diethyl sodiomalonate gave, after alkaline hydrolysis, 3α-cholestanylmalonic acid (XXIII), and thence 3α-cholestanylacetic acid (XXIV; R = H) (characterised as the crystalline methyl ester) which was different from 3β-cholestanylacetic acid (V; R = H) and from 3α-coprostanylacetic acid (VIII).



(XXII) (XXIII) (XXIV)

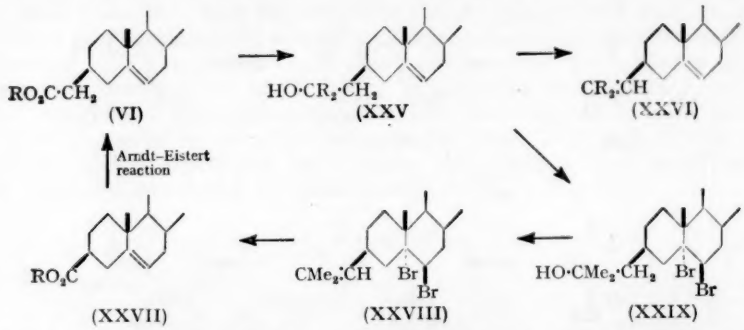
The foregoing partial syntheses establish the configurations of 3α-cholesterylacetic acid (VII; R = H) and 3α-cholestanylacetic acid (XXIV; R = H), and by exclusion those of 3β-cholesterylacetic acid (VI; R = H) and 3β-cholestanylacetic acid (V; R = H). The optical rotatory powers of these acids, their methyl esters, and the related primary alcohols are in agreement with these structures, since 3β-substituted cholestane compounds are invariably less dextrorotatory than the epimeric 3α-substituted derivatives (cf. Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd edn., 1949, p. 215) (see Table). The optical rotatory differences, although small, are definite, and our data are condensed from several determinations.

	$[M]_D$ of cholesteryl derivatives			$[M]_D$ of cholestanyl derivatives		
3-Substituent	3α	3β	Δ[3β − 3α]	3α	3β	Δ[3β − 3α]
$CH_2{\cdot}CO_2H$	−120°	−133°, −133° *	−13°	+121°	+99°	−22°
$CH_2{\cdot}CO_2Me$	−128	−141, −141 *	−13	+109	+86	−23
$CH_2{\cdot}CH_2{\cdot}OH$	−118	−128	−10	+105	+76	−29

* Baker and Petersen's values (*loc. cit.*).

3β-Cholesterylacetic acid has been degraded by a modification of the Wieland–Barbier method. Methyl 3β-cholesterylacetate (VI; R = Me), on treatment with phenylmagnesium bromide, gave the alcohol (XXV; R = Ph), dehydrated by refluxing acetic anhydride to the olefin (XXVI; R = Ph); this resisted oxidation by chromium trioxide

in acetic acid at 5—10°, and only after the modified method involving ozonolysis (see below) had been studied was it found that oxidation at 25° for 16 hr. yielded some 10% of cholest-5-ene-3β-carboxylic acid (XXVII; R = H). Methyl 3β-cholesterylacetate (VI; R = Me) was therefore transformed by treatment with methylmagnesium iodide into the alcohol (XXV; R = Me), dehydrated by thionyl chloride and pyridine to (XXVI; R = Me); the alcohol was converted into the 5α : 6β-dibromide (XXIX), which was dehydrated with thionyl chloride and pyridine to the 5 : 6-dibromo*iso*butene (XXVIII); ozonolysis, hydrolysis, oxidation, and debromination with zinc in aqueous acetic acid gave cholest-5-ene-3β-carboxylic acid (XXVII; R = H) (Marker's acid), isolated as the methyl ester.



We have also converted cholest-5-ene-3β-carboxylic acid (XXVII; R = H) (Marker's acid) into 3β-cholesterylacetic acid (VI; R = H) by the Arndt–Eistert reaction. This confirms the configurational identity, first established by Baker and Petersen and now shown to involve β-orientation, of the acids (VI and XXVII; R = H).

Methyl 3β-cholestanylacetate (V; R = Me) and methylmagnesium iodide or phenylmagnesium bromide similarly gave the appropriate alcohols and olefins; the latter, by ozonolysis and oxidation, yielded cholestane-3β-carboxylic acid, previously obtained by Marker *et al.* (*loc. cit.*) from cholest-5-ene-3β-carboxylic acid (XXVII; R = H) by hydrogenation. Also, 3α-cholestanylacetic acid has been degraded by the Wieland–Barbier procedure: the methyl ester and phenylmagnesium bromide gave the expected tertiary alcohol and thence the olefin, which was oxidised by chromium trioxide in acetic acid at 40° to cholestane-3α-carboxylic acid. This acid has unusual properties: it is soluble in pentane, and it cannot be extracted from ethereal solution with potassium hydroxide because its potassium salt is soluble in ether.

In conclusion, we refer briefly to the production, in the reaction of cholesteryl toluene-*p*-sulphonate (I) and diethyl sodiomalonate, of diethyl 3α-cholesterylmalonate (III). It has been shown that replacement reactions such as hydrolysis, acetolysis, etc., of cholesteryl chloride and toluene-*p*-sulphonate, and, more generally, of 3β-substitutedΔ^5-steroids, proceed with retention of configuration at $C_{(3)}$ or with rearrangement to 6β-substituted 3 : 5-*cyclo*-steroids (Shoppee, *J.*, **1946**, **1147**; Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Shoppee and Summers, *J.*, **1952**, **3361**). This was interpreted in terms of a unimolecular mechanism [S_N1] leading to a carbonium ion in which configuration was maintained at $C_{(3)}$ by intervention of the π-electrons of the 5 : 6-double bond. It now appears that, under suitable conditions and with appropriate nucleophiles, the unimolecular substitution [S_N1] leading to retention [(II)] or rearrangement [(IV)] may be accompanied by a bimolecular substitution [S_N2] leading to inversion [(III)]. We are investigating this new aspect.

Experimental

For general details see *J.*, **1953**, **243**. Neutralised aluminium oxide was used where stated (for preparation, see *J.*, **1953**, **543**). $[\alpha]_D$ are in $CHCl_3$ except where noted; ultra-violet absorption spectra were determined in EtOH on a Unicam SP. 500 spectrophotometer, with a corrected scale.

Cholest-5-en-3β-ylmalonic Acid.—This was prepared by Kaiser and Svarz's method (*J. Amer. Chem. Soc.*, **1945**, **67**, **1309**); we obtained identical results by the use of refluxing toluene, instead of xylene at 105°. To a solution of diethyl sodiomalonate, prepared by refluxing toluene (100 c.c.), sodium (3·45 g.) and diethyl malonate (27 c.c.) until all the sodium had dissolved, was added a solution of cholesteryl toluene-*p*-sulphonate (40 g.) (Wallis, Fernholz, and Gephart, *ibid.*, **1937**, **59**, **137**) in toluene (100 c.c.). Refluxing was continued for 16 hr., the solution was cooled, the precipitated sodium toluene-*p*-sulphonate was filtered off, washed with toluene, and the combined toluene extracts were evaporated under reduced pressure. The oil obtained was dissolved in ether and washed with water, and the solution was dried and evaporated. Attempts to separate the mixture of esters by chromatography were unsuccessful. Therefore the oil was refluxed with 5% methanolic potassium hydroxide (150 c.c.) for 16 hr. The precipitated potassium salt was dissolved in water (500 c.c.), and any non-acidic material removed in ether. After acidification with ice-cold 2N-sulphuric acid, the precipitated acid was extracted with ether, and the ethereal solution washed to neutrality, dried, evaporated to a small volume, and diluted with pentane. After 24 hr. at 0°, the precipitated crude cholest-5-en-3β-ylmalonic acid was filtered off (7 g., 8 g.), m. p. 160—170° (decomp.), $[\alpha]_D$ −28·5° (*c*, 1·6 in EtOH). Four recrystallisations from ether–pentane gave cholest-5-en-3β-ylmalonic acid, m. p. 205°, $[\alpha]_D$ −31° (*c*, 1·7 in EtOH). The dimethyl ester, prepared by using diazomethane in ether, crystallised from ether–methanol as colourless needles, m. p. 88—89°, to a turbid liquid clearing at 105°, $[\alpha]_D$ −29·5° (*c*, 1·7).

Cholest-5-en-3α- and -3β-ylacetic Acid.—These were prepared by heating the slightly impure cholest-5-en-3β-ylmalonic acid (m. p. 205°; 5 g.) at 205°/0·5 mm. until effervescence commenced. The temperature was then lowered to 170°, and after 30 min. the product was cooled, esterified with diazomethane, and crystallised from ether–methanol. This furnished material (860 mg.), m. p. 68—92°, which by recrystallisation from acetone gave methyl cholest-5-en-3α-ylacetate (250 mg.), m. p. 105—108°, $[\alpha]_D$ −29° (*c*, 1·8). Hydrolysis of the ester (100 mg.) by refluxing it for 2 hr. with 5% methanolic potassium hydroxide (15 c.c.) gave, after acidification, ether extraction, and crystallisation from acetone cholest-5-en-3α-ylacetic acid as needles, m. p. 205—210°, $[\alpha]_D$ −28° (*c*, 2·2). This is the "cholesteryl acetic acid" of Kaiser and Svarz (*J. Amer. Chem. Soc.*, **1945**, **67**, **1309**). The m. p. (70—74°) of the residual material (3·62 g.) (~80% overall yield from cholest-5-en-3β-ylmalonic acid) was not raised appreciably by recrystallisation, but a portion (700 mg.) was purified by chromatography on aluminium oxide (20 g.) in pentane. After elution with pentane–benzene (1 : 19 and 1 : 9; 70 c.c.) use of pentane–benzene (1 : 9; 70 c.c.) gave a solid (293 mg.) which, crystallised from ether–methanol, had m. p. 70—74°. Further elution with pentane–benzene (1 : 9; 3 × 70 c.c.) gave material (341 mg.), which by crystallisation from ether–methanol gave *methyl cholest-5-en-3β-ylacetate* as plates, m. p. 76—78°, $[\alpha]_D$ −32° (*c*, 1·6) (Found, after drying at 15°/0·02 mm. for 14 hr.: C, 81·3; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Further elution with the same eluant gave material melting over the range 63—70°. The ester (100 mg.) by hydrolysis for 2 hr. with 5% methanolic potassium hydroxide (15 c.c.), followed by acidification and extraction with ether, drying, evaporation, and recrystallisation from a concentrated acetone solution, gave *cholest-5-en-3β-ylacetic acid* as needles, m. p. 165—167°, $[\alpha]_D$ −31° (*c*, 1·4) (Found, after drying at 15°/0·02 mm. for 14 hr.: C, 80·9; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·3; H, 11·3%). The material (800 mg.) from the mother-liquor of the first recrystallisation of crude cholest-5-en-3β-ylmalonic acid, m. p. 160—170° (decomp.), was decarboxylated at 170°/0·5 mm. for 15 min. Crystallisation from acetone gave cholest-5-en-3α-ylacetic acid, m. p. 205—210°, identical with that obtained as above. The ratio of epimers present in the crude cholesterylmalonic acid of Kaiser and Svarz (*loc. cit.*) is therefore about 9 : 1, the β-epimer predominating.

2-(*Cholest-5-en-3β-yl*)*ethanol.*—To a solution of finely powdered lithium aluminium hydride (150 mg.) in ether (10 c.c.) was added a solution of methyl cholest-5-en-3β-ylacetate (150 mg.) in ether (10 c.c.). After 1 hour's refluxing excess of hydride was destroyed by ice and 2N-sulphuric acid. Extraction with ether, washing, drying, and evaporation gave an oil, which by crystallisation from ether–methanol gave 2-(*cholest-5-en-3β-yl*)*ethanol* (110 mg.) as colourless needles, m. p. 124—126°, $[\alpha]_D$ −31° (*c*, 3·2) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 83·3; H, 12·0. $C_{29}H_{50}O$ requires C, 84·0; H, 12·2%).

2-(*Cholest-5-en-3α-yl*)*ethanol.*—This was prepared as above from methyl 3α-cholesteryl-acetate (100 mg.) and lithium aluminium hydride (100 mg.) in ether (20 c.c.). Crystallisation from ether–methanol gave 2-(*cholest-5-en-3α-yl*)*ethanol* as colourless needles, m. p. 154—155°, $[\alpha]_D$ −28° (*c*, 1·8) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 83·6; H, 12·2%).

2-(*Cholest-5-en-3β-yl*)-1 : 1-*diphenylethanol.*—Methyl cholest-5-en-3β-ylacetate (300 mg.),

dried by azeotropic distillation with benzene and dissolved in ether (10 c.c.), was added to a solution of phenylmagnesium bromide prepared from ether (5 c.c.), bromobenzene (1·6 c.c.) and magnesium (330 mg.). After refluxing for 2 hr. the solution was cooled and poured into ice-cold saturated ammonium chloride solution, and the product extracted in ether, washed with 2N-sulphuric acid, water, and 2N-potassium hydroxide to neutrality, dried, and evaporated. Chromatography on aluminium oxide (10 g.) prepared in pentane, and elution with pentane (4 × 60 c.c.), gave a solid (containing bromobenzene) which crystallised from ether–methanol as plates, m. p. 65°, $\lambda_{max.}$ 213 (log ε 4·6) and 248 mμ (log ε 4·7), identified as diphenyl. Further elution with benzene–pentane (1 : 7, 5 × 60 c.c.) gave 2-(*cholest-5-en-3β-yl*)-1 : 1-*diphenylethanol* as needles (from ether–methanol) (330 mg., 90%), m. p. 149—150°, $[\alpha]_D$ −23°, (*c*, 1·0), $\lambda_{max.}$ 210 mμ (log ε 4·2) (Found, after drying at 100°/0·01 mm. for 4 hr. : C, 86·7; H, 10·3. $C_{41}H_{58}O$ requires C, 86·9; H, 10·3%).

2-(*Cholest-5-en-3β-yl*)-1 : 1-*diphenylethylene.*—To a solution of the foregoing ethanol (500 mg.) in pyridine (10 c.c.) was added thionyl chloride (1·5 c.c.) with ice-cooling. After 1 hr. excess of thionyl chloride was destroyed by ice, the product extracted with ether, and the ethereal solution washed with 2N-hydrochloric acid and with water. The *ethylene* crystallised from ether–methanol as needles, m. p. 183—184°, $[\alpha]_D$ 0° (*c*, 1·0), $\lambda_{max.}$ 210 (log ε 4·3) and 253 mμ (log ε 4·2) (Found, after drying at 90°/0·03 mm. for 3 hr. : C, 89·3; H, 10·4. $C_{41}H_{56}$ requires C, 89·7; H, 10·3%).

Cholest-5-ene-3β-carboxylic Acid.—Attempts to oxidise 2-(cholest-5-en-3β-yl)-1 : 1-diphenylethylene by chromium trioxide–acetic acid at 5° (winter) failed to give the required acid; after the discovery that ozonolysis of 2-(cholest-5-en-3β-yl)-1 : 1-dimethylethylene as its 5α : 6β-dibromide gave (after debromination) cholest-5-ene-3β-carboxylic acid, it was found that chromium trioxide–acetic acid was effective to some extent at 15—20° (summer). (Cholest-5-en-3β-yl)-1 : 1-diphenylethylene (160 mg.) was oxidised in dioxan (30 c.c.) with chromium trioxide (270 mg.) in acetic acid (20 c.c.). After 16 hr. excess of trioxide was destroyed by methanol, and solvents were removed under reduced pressure. Addition of 2N-sulphuric acid and extraction with ether gave a sticky solid, which when triturated with pentane gave an insoluble acidic residue (10 mg.); this was cholest-5-ene-3β-carboxylic acid, m. p. 218—220°, giving no m. p. depression with the acid obtained by treatment of cholesterylmagnesium bromide with carbon dioxide. The pentane-soluble portion, crystallised from ether–methanol, had m. p. 183° and gave no m. p. depression with the starting material.

2-(*Cholest-5-en-3β-yl*)-1 : 1-*dimethylethanol.*—Methyl cholest-5-en-3β-ylacetate (1·33 g.) in benzene (20 c.c.) was added to a solution of methylmagnesium iodide, prepared from methyl iodide (4·5 c.c.), magnesium (1·7 g.), and ether (40 c.c.), the mixture refluxed for 2 hr., and poured into cold saturated ammonium chloride solution (200 c.c.). Extraction with ether followed by washing with 2N-sulphuric acid, water, and dilute sodium thiosulphate solution, and drying, gave 2-(*cholest-5-en-3β-yl*)-1 : 1-*dimethylethanol* as colourless prisms (from ether–methanol), m. p. 158—160°, $[\alpha]_D$ −26° (*c*, 1·8) (Found, after drying at 70°/0·01 mm. for 5 hr. : C, 83·7, 84·0; H, 12·2, 12·3. $C_{31}H_{54}O$ requires C, 84·1; H, 12·3%).

2-(*Cholest-5-en-3β-yl*)-1 : 1-*dimethylethylene.*—To a solution of 2-(cholest-5-en-3β-yl)-1 : 1-dimethylethanol (387 mg.) in pyridine (4 c.c.) was added thionyl chloride (0·5 c.c.) with cooling. After 20 min. the solvents were removed under reduced pressure, water was added, and the residue extracted with ether. By the usual procedure the ethylene was obtained as a brown oil (310 mg.). An attempt to oxidise the hydrocarbon (100 mg.) in ether (6 c.c.) with a 2% solution of chromium trioxide in acetic acid (3 c.c.) at 5° for 16 hr. gave no acidic material, and the neutral portion (89 mg.) was an oil.

2-(5α : 6β-*Dibromocholestan*-3β-*yl*)-1 : 1-*dimethylethanol.*—This was prepared by adding bromine (300 mg.) in ether (12 c.c.) to a solution of 2-(cholest-5-en-3β-yl)-1 : 1-dimethylethanol (680 mg.) in ether (20 c.c.). After 1·5 hr. at 5°, the solvent was removed under reduced pressure. Crystallisation from ether–methanol gave 2-(5α : 6β-dibromocholestan-3β-yl)-1 : 1-dimethylethanol as needles, m. p. 59—62°, decomposing over a period of hours at room temperature. The dibromo-compound was therefore not usually isolated.

2-(5α : 6β-*Dibromocholestan*-3β-*yl*)-1 : 1-*dimethylethylene.*—Dehydration of the dibromocholestanylethanol (prepared from 680 mg. of the alcohol) in pyridine (5 c.c.) was carried out at 0° with thionyl chloride (2 c.c.). After 15 min. the temperature was allowed to rise to 15° for a further 15 min. and the excess of thionyl chloride was then decomposed. After extraction with ether followed by the usual washing and drying, solvent was removed under reduced pressure, to yield 2-(5α : 6β-dibromocholestan-3β-yl)-1 : 1-dimethylethylene as a brown oil.

Methyl Cholest-5-ene-3β-carboxylate.—The 5α : 6β-dibromo-hydrocarbon obtained in the

previous reaction was dissolved in ethyl acetate (100 c.c.), cooled in solid carbon dioxide–acetone, and a current of ozonised oxygen was passed in for 0·5 hr. After a further 0·5 hr. at −70°, solvent was removed under reduced pressure, the oil was dissolved in acetic acid (90 c.c.), and water (10 c.c.) and zinc dust (2·5 g.) were added. The mixture was refluxed for 0·5 hr. and, after removal of the solvents under reduced pressure, the residue was extracted with ether, and the ether extracts were washed with 2N-sulphuric acid. Extraction of the acidic material with two portions of N-potassium hydroxide, acidification, and ether-extraction gave a solid acid (162 mg.). This was esterified with diazomethane and chromatographed on a column of neutralised aluminium oxide (5 g.) prepared in pentane. Elution with benzene–pentane (3 : 7; 4 × 15 c.c.) gave a solid (90 mg.), which crystallised from ether–methanol to yield methyl cholest-5-ene-3β-carboxylate as colourless needles, m. p. 99—100°, giving no depression on admixture with a sample prepared by treatment of cholesterylmagnesium bromide with carbon dioxide. Further elution with benzene (15 c.c.) and ether (15 c.c.) gave only oils.

Methyl 3β-Cholestanylacetate.—Methyl cholest-5-en-3β-ylacetate (1·5 g.), in acetic acid (250 c.c.), was shaken in hydrogen with platinum oxide (200 mg.) for 20 min. (theoretical absorption in 10 min.). After removal of the solvent and catalyst, crystallisation from ether–methanol gave methyl 3β-cholestanylacetate, m. p. 78—82°, $[\alpha]_D$ +16° (*c*, 3·6). 3β-Cholestanylacetic acid, prepared from the ester by methanolic N-potassium hydroxide, crystallised from acetone as colourless needles, m. p. 170—172°, $[\alpha]_D$ +18° (*c*, 2·3). Both the acid and its ester so prepared gave a faint yellow colour with tetranitromethane–chloroform. The unsaturated impurities were removed by dissolving crude methyl 3β-cholestanylacetate (675 mg.) in benzene (10 c.c.) and adding a mixture of formic acid (98%; 5 c.c.) and hydrogen peroxide (100-vol.; 4 c.c.). The mixture was warmed to 40° and shaken occasionally; after 3 hr., ether was added and the solution washed to neutrality. Drying and evaporation gave a solid which after filtration in pentane through aluminium oxide gave *methyl 3β-cholestanylacetate* (669 mg.), which crystallised from ether–methanol as plates, m. p. 85°, $[\alpha]_D$ +20° (*c*, 1·7), giving no colour with tetranitromethane (Found, after drying at 15°/0·03 mm. for 18 hr.: C, 81·0; H, 11·8. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). Treatment of the mother-liquors from the first crystallisation of the ester gave a further quantity (250 mg.) of pure methyl 3β-cholestanylacetate.

3β-Cholestanylacetic Acid.—3β-Cholestanylacetic acid was prepared by refluxing methyl 3β-cholestanyl acetate (100 mg.) in methanolic N-potassium hydroxide (15 c.c.) for 2 hr. Acidification and ether-extraction gave *3β-cholestanylacetic acid* as needles (from acetone), m. p. 177°, $[\alpha]_D$ +23° (*c*, 1·1) (Found, after drying at 100°/0·01 mm. for 4 hr.: C, 80·7; H, 11·6. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%).

2-(3β-Cholestanyl)ethanol.—This was prepared by adding a solution of lithium aluminium hydride (150 mg.) in ether (15 c.c.) to a solution of methyl 3β-cholestanyl acetate (104 mg.) in ether (10 c.c.). After 1 hour's refluxing, excess of lithium aluminium hydride was decomposed with cold 2N-sulphuric acid, and the product extracted with ether. Drying and evaporation gave *2-(3β-cholestanyl)ethanol*, which crystallised as needles, m. p. 119—121°, $[\alpha]_D$ +18° (*c*, 2·7), from ether–methanol (Found, after drying at 15°/0·03 mm. for 18 hr.: C, 83·4; H, 12·5. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%). Alternatively, 2-(cholest-5-en-3β-yl)ethanol (25 mg.; m. p. 124—126°) was shaken in acetic acid (20 c.c.) in hydrogen with platinum oxide (15 mg.) for 1 hr. After removal of the catalyst and solvent, 2-(3β-cholestanyl)ethanol was obtained as needles (from ether–methanol), m. p. 118—120°, giving no depression by admixture with the previous preparation.

2-(3β-Cholestanyl)-1 : 1-dimethylethanol.—A solution of methyl 3β-cholestanylacetate (500 mg.; dried by azeotropic distillation with benzene), dissolved in benzene (5 c.c.), was added to methylmagnesium iodide, prepared from methyl iodide (1·5 c.c.), magnesium (560 mg.), and ether (12 c.c.). After 2 hours' refluxing, the solution was cooled and poured into cold saturated ammonium chloride solution (100 c.c.). Extraction with ether, followed by washing and drying, yielded *2-(3β-cholestanyl)-1 : 1-dimethylethanol*, which crystallised from ether–methanol as needles, double m. p. 110°/128°, $[\alpha]_D$ +23° (*c*, 1·4) (Found, after drying at 15°/0·02 mm. for 12 hr.: C, 83·4; H, 12·7. $C_{31}H_{56}O$ requires C, 83·7; H, 12·7%).

2-(3β-Cholestanyl)-1 : 1-dimethylethylene.—2-(3β-Cholestanyl)-1 : 1-dimethylethanol (460 mg.) in benzene (8 c.c.) and pyridine (0·5 c.c.) was treated with thionyl chloride (0·5 c.c.), and the mixture was kept at 15° for 0·5 hr. Excess of thionyl chloride was destroyed by ice, and the product extracted with ether. The ethereal extract gave, after washing, drying, and evaporation, a brown oil (406 mg.) which, after filtration through a column of aluminium oxide (15 g.) prepared in pentane, afforded a colourless solid (360 mg.), which crystallised from

ether–methanol to give 2-(3β-cholestanyl)-1 : 1-dimethylethylene as prisms, m. p. 96—98°, $[\alpha]_D$ +21° (*c*, 1·5) (Found, after drying at 15°/0·02 mm. for 12 hr. : C, 86·2; H, 12·8. $C_{31}H_{54}$ requires C, 87·2; H, 12·8%). An attempt was made to oxidise this hydrocarbon by using chromium trioxide in acetic acid; to the hydrocarbon (160 mg.) in ether (6 c.c.) was added a 2% solution of chromium trioxide in acetic acid (4 c.c.), and the mixture was kept overnight at 5°. No acidic material was produced; the neutral product (150 mg.), crystallised from ether–methanol, had m. p. 90—92° and gave no depression on admixture with starting material.

Cholestane-3β-carboxylic Acid.—A solution of 2-(cholestan-3β-yl)-1 : 1-dimethylethylene (170 mg.) in ether (3 c.c.) and acetic acid (40 c.c.) was treated with ozonised oxygen for 0·5 hr. at 20°. Water (4 c.c.) was then added and the mixture refluxed for 0·5 hr.; after removal of the solvents under reduced pressure, the oily residue was dissolved in ether (5 c.c.), and a 2% solution of chromium trioxide in acetic acid (3 c.c.) added. The mixture was set aside at 15° for 16 hr. and methanol added before removal of the solvents under reduced pressure. After acidification with 2N-sulphuric acid, the product was extracted with ether and the ethereal extract shaken with 3 portions of N-potassium hydroxide. This alkaline extract was acidified and extracted with ether; drying and evaporation of the solvent gave cholestane-3β-carboxylic acid (36 mg.), which crystallised from ether–pentane as needles, m. p. 204—207°. A mixed m. p. with cholestane-3β-carboxylic acid (prepared by the catalytic hydrogenation of methyl cholest-5-ene-3β-carboxylate and subsequent alkaline hydrolysis) showed no depression.

2-(3β-*Cholestanyl*)-1 : 1-*diphenylethanol.*—Methyl 3β-cholestanylacetate (500 mg.) dried by azeotropic distillation with benzene, was dissolved in ether (10 c.c.) and added to a solution of phenylmagnesium bromide, prepared from bromobenzene (2·3 c.c.), ether (10 c.c.), and magnesium (0·53 g.). After standing for 4 hr. at 15° the mixture was poured into a cold saturated ammonium chloride solution (100 c.c.). Extraction with ether, followed by washing of the extract with 2N-sulphuric acid and N-potassium hydroxide, drying, and evaporation, gave a solid which even after several crystallisations appeared to melt over a wide temperature range. The material at 160°/0·02 mm. gave a sublimate (24 mg.), m. p. 50—58° (? diphenyl), whilst the residue, after crystallisation from ether–methanol, gave 2-(3β-*cholestanyl*)-1 : 1-*diphenylethanol* as needles, double m. p. 94°/157°, $[\alpha]_D$ +13·5 (*c*, 1·4) (Found, after drying at 15°/0·02 mm. for 12 hr. : C, 85·35; H, 10·2. $C_{41}H_{60}O$ requires C, 86·5; H, 10·6%). The poor analytical result probably arises through retention of some methanol of crystallisation.

2-(3β-*Cholestanyl*)-1 : 1-*diphenylethylene.*—2-(3β-Cholestanyl)-1 : 1-diphenylethanol (230 mg.) was refluxed with acetic anhydride (10 c.c.) for 15 min. Removal of the reagent under reduced pressure gave 2-(3β-*cholestanyl*)-1 : 1-*diphenylethylene* as needles (185 mg.) (from ether–methanol), m. p. 173°, $[\alpha]_D$ +4° (*c*, 2·8) (Found, after drying at 15°/0·02 mm. for 12 hr. : C, 89·2; H, 10·4. $C_{41}H_{58}$ requires C, 89·4; H, 10·6%).

Cholestane-3β-carboxylic Acid.—A solution of 2-(3β-cholestanyl)-1 : 1-diphenylethylene (136 mg.) in ethyl acetate (50 c.c.) was treated with ozonised oxygen at −70° for 15 min. After 20 min. at room temperature, the solvent was removed under reduced pressure. The resulting oil was dissolved in acetic acid (30 c.c.), and water (1 c.c.) was added. After 1 hr. at 100° the solvents were removed in a vacuum, the oily product was dissolved in ether (5 c.c.), and a 2% solution of chromium trioxide in acetic acid (1·5 c.c.) was added; after 12 hr., methanol was added and solvents were again removed. The residue was treated with 2N-sulphuric acid and extracted with ether. Shaking the ethereal extract with N-potassium hydroxide gave after acidification and ether-extraction cholestane-3β-carboxylic acid (30 mg.), m. p. 210°, identical with the acid prepared from 2-(3β-cholestanyl)-1 : 1-dimethylethylene. This was esterified with diazomethane and chromatographed on neutralised aluminium oxide (3 g.) prepared in pentane. Elution with benzene–pentane (1 : 19; 2 × 3 c.c.) yielded oil (2·5 mg.) but use of benzene–pentane (3 : 7, 1 × 3 c.c.; and 2 : 3, 1 × 3 c.c.) yielded an oil (23 mg.), which crystallised from ether–methanol in needles, m. p. 64—69°, identical with methyl cholestane-3β-carboxylate prepared by hydrogenation of methyl cholest-5-ene-3β-carboxylate.

Methyl Cholest-5-en-3β-ylacetate.—Cholest-5-ene-3β-carboxylic acid (250 mg.; dried by azeotropic distillation with benzene) was dissolved in pyridine (2 c.c.) and benzene (25 c.c.); thionyl chloride (0·5 c.c.) was then added and the solution was kept at 0° for 30 min. The solution was then warmed at 40° for 10 min. and the solvents were removed under reduced pressure. A further quantity of benzene (5 c.c.) was then added and the mixture again evaporated completely in a vacuum. The acid chloride, dissolved in benzene (10 c.c.), was then filtered into an excess of dry ethereal diazomethane. After 1 hr. at 15° the solution was evaporated to dryness and the residual solid warmed with methanol (40 c.c.) and freshly prepared

silver oxide (150 mg.). After 10 min. at 50° the solution was refluxed and small quantities of silver oxide (totalling 150 mg.) were added periodically during 40 min. After removal of silver oxide and methanol, the oil was chromatographed on a column of neutralised aluminium oxide prepared in pentane. Elution with benzene–pentane (1 : 9; 1 × 20 c.c.) gave a trace of oil whilst use of benzene–pentane (3 : 17; 1 × 20 c.c.) gave a solid (25 mg.), m. p. 66—71°. Further elution with benzene–pentane (3 : 17; 4 × 20 c.c.) gave a solid (49 mg.), which, crystallised from ether–methanol, yielded methyl cholest-5-en-3β-ylacetate, m. p. 76—78°. No depression of m. p. was observed by admixture with methyl cholest-5-en-3β-ylacetate prepared by decarboxylation of cholest-5-en-3β-ylmalonic acid.

6-Oxocholestan-3β-yl Toluene-p-sulphonate.—6-Nitrocholesteryl acetate, m. p. 100—103°, was prepared by the procedure of Shoppee and Summers (*J.*, 1952, 3361), and converted by treatment with zinc–acetic acid into 3β-acetoxycholestan-6-one, m. p. 129°, hydrolysed by hot methanolic N-potassium hydroxide to 3β-hydroxycholestan-6-one, double m. p. 142°/149°. The hydroxy-ketone (25 g.; dried at 20°/0·01 mm.) was dissolved in pyridine (125 c.c.) and treated with purified toluene-*p*-sulphonyl chloride (25 g.); after standing for 16 hr. at 25°, most of the pyridine was removed under reduced pressure. The product was extracted with chloroform, and, after being washed in the usual manner, was isolated and recrystallised from acetone, to give 6-oxocholestan-3β-yl toluene-*p*-sulphonate as cubic prisms, m. p. 180° (decomp.) (cf. Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424, who record 169—179°).

6-Oxocholestan-3α-ylmalonic Acid.—A solution of diethyl sodiomalonate was prepared by refluxing sodium (2·13 g.), toluene (125 c.c.), and diethyl malonate (23 c.c.), and a solution of 6-oxocholestan-3β-yl toluene-*p*-sulphonate (23 g.) in toluene (130 c.c.) was added and refluxing continued for 72 hr. The precipitated sodium toluene-*p*-sulphonate was filtered off and washed with toluene, and the combined toluene extracts were evaporated to dryness under reduced pressure. The residual oil was dissolved in ether, washed with water, dried, and evaporated. Hydrolysis was carried out with boiling methanolic N-potassium hydroxide (125 c.c.) for 16 hr. The precipitated potassium salt was filtered off and shaken with water and ether, to remove any non-acidic impurities; the aqueous layer, after acidification and extraction of the precipitated acid with ether, gave *6-oxocholestan-3α-ylmalonic acid* (8·2 g.), which crystallised from ether–pentane as the dihydrate, m. p. 179° (decomp.), $[\alpha]_D$ −30° (*c*, 1·6) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 68·6; H, 9·9. $C_{30}H_{48}O_5,2H_2O$ requires C, 68·7; H, 10·0%). The *dimethyl ester*, prepared with diazomethane, crystallised from ether–methanol as needles, m. p. 129—131°, $[\alpha]_D$ −31° (*c*, 1·6) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 74·3; H, 10·3. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·1%). The methanolic potassium hydroxide solution obtained after filtration of the potassium salt gave only a trace of oily acid when diluted with water and extracted with ether. The neutral ethereal extracts were combined, washed, dried, and evaporated, and the residue was warmed with methanol. The methanol-soluble portion crystallised as plates, m. p. 90—94°, identified as 3 : 5-*cyclo*cholestan-6-one (8 g.), the normal 3 : 5-elimination product obtained by the action of potassium hydroxide on 3β-toluene-*p*-sulphonyloxycholestan-6-one. The methanol-insoluble portion, after several crystallisations from dioxan, gave an unidentified *substance* as needles (2 g.), m. p. 186°, $[\alpha]_D$ +3·5° (*c*, 1·2); the infra-red spectrum shows a maximum at 1710 cm.$^{-1}$, characteristic of an unconjugated carbonyl group in a six-membered ring, whilst a faint colouration with tetranitromethane may be due to the presence of a double bond (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 77·5; H, 10·7. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%). The structure of this compound is being investigated.

Treatment of 3 : 5-cyclo*Cholestan-6-one with Diethyl Sodiomalonate.*—3 : 5-*cyclo*Cholestan-6-one (2 g.) in toluene (10 c.c.) was added to a solution of diethyl sodiomalonate [from diethyl malonate (2·8 c.c.) and sodium (0·26 g.) in toluene (20 c.c.)], and the whole was refluxed for 72 hr. The solvent was removed in a vacuum, and the product heated with methanolic 2N-potassium hydroxide (50 c.c.) for 3 hr. After saturation with carbon dioxide, removal of methanol in a vacuum, and addition of water, the product was extracted with ether and separated into acidic and neutral fractions. The former gave no insoluble acidic material by acidification of the aqueous alkaline solution; the latter gave 3 : 5-*cyclo*cholestan-6-one (85%), m. p. 90—94° after crystallisation from methanol, identical with the starting material.

6-Oxocholestan-3α-ylacetic Acid.—6-Oxocholestan-3α-ylmalonic acid was decarboxylated at 160—170°/0·5 mm. (1 hr.). The product was crystallised from ether–pentane, to give *6-oxocholestan-3α-ylacetic acid* as needles (7·8 g.), m. p. 171—173°, $[\alpha]_D$ −28° (*c*, 1·5) (Found, after drying at 70°/0·01 mm. for 5 hr.: C, 78·3; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). The acid (5·8 g.) with an excess of ethereal diazomethane gave *methyl 6-oxocholestan-3α-ylacetate* as needles (5·3 g.) (from acetone), m. p. 116°, $[\alpha]_D$ −28° (*c*, 1·3) [Found, (*a*) after sub-

limation at 120°/0·05 mm., (*b*) after drying at 70°/0·01 mm. for 5 hr. : C, 78·9, 78·0; H, 10·8, 10·8. $C_{30}H_{50}O_3$ requires C, 78·6; H, 11·0%].

Methyl 6β-*Hydroxycholestan*-3α-*ylacetate*.—The keto-ester was dissolved in methanol (25 c.c.) and ether (5 c.c.), a solution of sodium borohydride (85 mg.) in water (2 c.c.) and methanol (15 c.c.) was added, and the mixture was kept at 15° for 30 min. Excess of sodium borohydride was destroyed by the addition of a little 2N-sulphuric acid, and the product extracted with ether. The ethereal extract was washed, dried, and completely evaporated in a high vacuum, but methyl 6β-hydroxycholestan-3α-ylacetate failed to crystallise and was extremely soluble in the usual solvents. Chromatography of the product (995 mg.) on neutralised aluminium oxide gave only oils.

2-(6β-*Hydroxycholestan*-3α-*yl*)*ethanol*.—(*a*) A suspension of finely powdered lithium aluminium hydride (1 g.) in ether (50 c.c.) was added to a solution of methyl 6-oxocholestan-3α-ylacetate (1 g.) in ether (100 c.c.). The mixture was kept at 15° for 15 min. and then refluxed for 30 min. Excess of hydride was decomposed by adding ice and 2N-sulphuric acid, and the product extracted with ether. The ether extract was washed, dried, and evaporated, to yield 2-(6β-*hydroxycholestan*-3α-*yl*)*ethanol*, which crystallised from ether–pentane as plates (470 mg.), m. p. 155—157°, $[\alpha]_D$ +23° (*c*, 1·2) (Found, after sublimation at 150°/0·05 mm. : C, 80·1; H, 11·9. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%). The *diacetate* was prepared from the diol (110 mg.) with pyridine (2 c.c.) and acetic anhydride (0·5 c.c.) at 15° for 15 hr., and crystallised from ether–methanol as prisms, m. p. 98—101°, $[\alpha]_D$ +11° (*c*, 1·9) (Found, after sublimation at 100°/0·01 mm. : C, 76·5; H, 11·0. $C_{33}H_{56}O_4$ requires C, 76·7; H, 10·9%).

(*b*) Methyl 6β-hydroxycholestan-3α-ylacetate (64 mg.) in ether (10 c.c.) was refluxed for 10 min. with a solution of lithium aluminium hydride (100 mg.) in ether (5 c.c.). The product was extracted as in (*a*) above. Crystallisation from ether–pentane gave 2-(6β-hydroxycholestan-3α-yl)ethanol, identical with that obtained as in (*a*).

6β-*Hydroxycholestan*-3α-*ylacetic Acid*.—The methyl hydroxy-ester (217 mg.) was hydrolysed for 1 hr. with boiling methanolic 0·5N-potassium hydroxide (20 c.c.). Dilution with water, followed by acidification and the usual ether-extraction, gave 6β-*hydroxycholestan*-3α-*ylacetic acid*, which crystallised from ether–pentane as needles (188 mg.), m. p. 168—171°, $[\alpha]_D$ +31° (*c*, 1·5) (Found, after drying at 90°/0·03 mm. for 3 hr. : C, 77·6; H, 11·3. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

6β-*Acetoxycholestan*-3α-*ylacetic Acid*.—The hydroxy-acid (403 mg.) with pyridine (4 c.c.) and acetic anhydride (4 c.c.) at 15° for 16 hr. gave 6β-*acetoxycholestan*-3α-*ylacetic acid* as an amorphous solid which could not be crystallised, $[\alpha]_D$ +8° (*c*, 0·8) (Found, after drying at 10°/0·01 mm. for 12 hr. : C, 76·2; H, 10·7. $C_{31}H_{52}O_4$ requires C, 76·2; H, 10·7%).

Methyl Cholest-5-*en*-3α-*ylacetate*.—Methyl 6β-hydroxycholestan-3α-ylacetate (156 mg.), dissolved in pyridine (2·5 c.c.), was treated with phosphorus oxychloride (0·3 c.c.). After 1 hr. at 15° the solution was diluted with water, and the product extracted with ether. The ethereal solution was washed, dried, and evaporated, and the product was chromatographed on aluminium oxide (6 g.) prepared in pentane. Elution with benzene–pentane (1 : 1; 1 × 10 c.c.) gave a sticky solid but further elution with benzene–pentane (1 : 1; 4 × 10 c.c.) gave a solid (64 mg.) which, crystallised twice from acetone, yielded methyl cholest-5-en-3α-ylacetate, m. p. 104—108°, giving a yellow colour with tetranitromethane in chloroform; no depression of m. p. was observed on admixture with a specimen of methyl cholest-5-en-3α-ylacetate isolated from the decarboxylation of crude cholest-5-en-3β-ylmalonic acid.

3α-*Coprostanylacetic Acid*.—Methyl cholest-5-en-3α-ylacetate (52 mg.), dissolved in acetic acid (6 c.c.) and ethyl acetate (4 c.c.) containing a trace of perchloric acid, was shaken in hydrogen with platinum oxide (170 mg.) for 3 hr. Removal of solvents and catalyst furnished an oil, which after hydrolysis with hot 2N-methanolic potassium hydroxide for 2 hr. gave an acid. This was isolated in the usual manner and recrystallised from acetone and then from ether–pentane, to yield 3α-*coprostanylacetic acid* (16 mg.), m. p. 150—152°, $[\alpha]_D$ +33° (*c*, 0·9) (Found, after sublimation at 160°/0·01 mm. : C, 80·9; H, 11·7. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%).

6β-*Hydroxycholestan*-3β-*yl Toluene*-p-*sulphonate*.—6-Oxocholestan-3β-yl toluene-*p*-sulphonate (10·3 g.) in dioxan (150 c.c.) was treated with a solution of sodium borohydride (785 mg., 1·2 mol.) in water (1 c.c.) and methanol (100 c.c.). After 1·5 hr. at 30° gas evolution had ceased; dilution with an equal volume of water furnished a solid which, after filtration, washing with water, and drying, was recrystallised from ether–pentane to give 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate, double m. p. 140°/160° (decomp.), $[\alpha]_D$ −9° (*c*, 1·9) (8·83 g., 85%) (cf. Reich and Lardon, *Helv. Chim. Acta*, 1946, **29**, 671, who give double m. p. 139°/150°). The compound was

identical with a sample previously prepared by Dr. G. H. R. Summers from cholestane-3β : 6β-diol by treatment with toluene-*p*-sulphonyl chloride (1 mol.) in pyridine at 15°.

6β-*Hydroxycholestan*-3α-*ylmalonic Acid.*—(*a*) To a solution of diethyl sodiomalonate prepared from sodium (0·86 g.) and diethyl malonate (6·8 c.c.) in toluene (50 c.c.), was added a solution of 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (7·5 g.) in toluene (50 c.c.). After 72 hours' refluxing the precipitated sodium toluene-*p*-sulphonate was filtered off and washed with toluene, the combined toluene extracts were evaporated to dryness in a vacuum, and the residue was refluxed for 3 hr. with methanolic 2N-potassium hydroxide. Dilution with water, ether-extraction of non-acidic material, acidification of the aqueous layer, ether-extraction, and the usual working up, gave 6β-*hydroxycholestan*-3α-*ylmalonic acid*, m. p. 168—170° (decomp.), $[\alpha]_D$ +9° (*c*, 1·6), obtained as a microcrystalline powder from ether–pentane (Found, after drying at 40°/0·02 mm. for 12 hr.: C, 69·8; H, 10·1. $C_{30}H_{50}O_5,1\frac{1}{2}H_2O$ requires C, 69·6; H, 10·3%). The *dimethyl ester*, although crystalline, $[\alpha]_D$ +7° (*c*, 1·4), was soluble in all the usual solvents and could not satisfactorily be recrystallised. A sample sublimed at 180°/0·02 mm. had m.p. 108—113° (Found: C, 74·1; H, 10·6. $C_{32}H_{54}O_5$ requires C, 74·1; H, 10·6%).

(*b*) Dimethyl 6-oxocholestan-3α-ylmalonate (1·27 g.) was suspended in methanol (50 c.c.), and a solution of sodium borohydride (103 mg.) in water (2 c.c.) and methanol (10 c.c.) added. The solid dissolved and after 30 min. potassium hydroxide (3 g.) was added, and the mixture refluxed for 30 min. Acidification and ether-extraction gave, after the usual working up, 6β-hydroxycholestan-3α-ylmalonic acid, m. p. 168—170° (decomp.), giving no depression of m. p. with material prepared by method (*a*).

Dimethyl Cholest-5-en-3α-*ylmalonate.*—Dimethyl 6β-hydroxycholestan-3α-ylmalonate (1 g.) in pyridine (10 c.c.) was treated with phosphorus oxychloride (1 c.c.) at 0°. After 5 hr. at 15°, the mixture was poured into ice-water, and the product extracted with ether. The extract was worked up, to give an oil (750 mg.), of which a portion (390 mg.) was chromatographed on neutralised aluminium oxide (12 g.) prepared in benzene–pentane (1 : 1). Elution with benzene–pentane (1 : 1; 2 × 40 c.c.) gave an oil (29 mg.), whilst use of benzene–pentane (7 : 3; 40 c.c.) yielded partly crystalline material (32 mg.); further elution with benzene–pentane (7 : 3, 40 c.c.; 4 : 1, 3 × 40 c.c.) afforded a solid (140 mg.), which recrystallised from methanol to give *dimethyl cholest-5-en*-3α-*ylmalonate*, m. p. 118°, $[\alpha]_D$ −49° (*c*, 1·4) (Found, after sublimation at 160°/0·02 mm.: C, 76·9; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·8; H, 10·5%). Further elution with benzene, ether, and methanol gave oils.

Cholest-5-en-3α-*ylmalonic Acid.*—The above dimethyl ester (50 mg.) was refluxed with methanolic 2N-potassium hydroxide (10 c.c.) for 2 hr. After removal of part of the methanol in a vacuum, dilution with water, and extraction of any neutral material with ether, acidification of the alkaline solution gave a solid acid. Crystallisation from ether–pentane gave *cholest-5-en*-3α-*ylmalonic acid* (25 mg.), m. p. 190° (decomp.), $[\alpha]_D$ −36° (*c*, 1·10 in EtOH) (Found, after drying at 40°/0·02 mm. for 12 hr.: C, 74·3; H, 10·1. $C_{35}H_{46}O_4,\frac{1}{2}H_2O$ requires C, 74·8; H, 10·3%).

Cholest-5-en-3α-*ylacetic Acid.*—Decarboxylation of cholest-5-en-3α-ylmalonic acid at 200°/0·01 mm., followed by sublimation of the product at 200—210°/0·01 mm., gave cholest-5-en-3α-ylacetic acid as needles (from acetone), m. p. 205—208°, mixed m. p. 205—208° with specimens obtained by other methods (see above).

3α-*Cholestanylmalonic Acid.*—To a solution of diethyl sodiomalonate, prepared from sodium (3·45 g.) and diethyl malonate (27 c.c.) in toluene (150 c.c.), was added 3β-cholestanyl toluene-*p*-sulphonate (28 g.) in toluene (200 c.c.). After 72 hours' refluxing the mixture was cooled, sodium toluene-*p*-sulphonate was filtered off, the filtrate evaporated in a vacuum, and the residual oil hydrolysed with potassium hydroxide (20 g.) in methanol (150 c.c.) and *iso*propanol (200 c.c.). After 3 hr. the suspension was cooled, and the precipitated potassium salt was collected and converted into the free acid; recrystallisation from ether–pentane gave 3α-*cholestanylmalonic acid*, m. p. 193° (decomp.), $[\alpha]_D$ +30° (*c*, 1·6 in EtOH) (12·5 g.) (Found, after drying at 40°/0·02 mm. for 12 hr.: C, 76·0; H, 10·7. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). The *dimethyl ester*, prepared by ethereal diazomethane and recrystallised from ether–methanol, had m. p. 147°, $[\alpha]_D$ +20° (*c*, 1·80) (Found, after sublimation at 160°/0·01 mm.: C, 76·3; H, 10·7. $C_{32}H_{54}O_4$ requires C, 76·4; H, 10·8%).

3α-*Cholestanylacetic Acid.*—3α-Cholestanylmalonic acid (11·5 g.) was decarboxylated at 215°/760 mm. for 15 min.; the product on crystallisation from ether–acetone gave 3α-*cholestanylacetic acid*, m. p. 210°, $[\alpha]_D$ +24·5° (*c*, 1·91) (Found, after sublimation at 200°/0·01 mm.: C, 80·4; H, 11·5. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%). The *methyl ester*, prepared by ethereal diazomethane and crystallised from ether–methanol, had m. p. 118°, $[\alpha]_D$ +28° (*c*, 1·51)

(Found, after sublimation at 160°/0·01 mm.: C, 80·8; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

2-(3α-*Cholestanyl*)*ethanol*.—Methyl 3α-cholestanylacetate (100 mg.) was refluxed with lithium aluminium hydride (100 mg.) in ether (20 c.c.) for 15 min. Excess of the reagent was destroyed by addition of water, and the product isolated in the usual way. Crystallisation from methanol gave 2-(3α-*cholestanyl*)*ethanol* (92 mg.), m. p. 111°, $[\alpha]_D$ +25° (*c*, 1·3) (Found, after sublimation at 160°/0·01 mm.: C, 83·8; H, 12·3. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%).

2-(3α-*Cholestanyl*)-1 : 1-*diphenylethanol*.—Methyl 3α-cholestanylacetate (9 g.; dried by azeotropic distillation with benzene), dissolved in benzene (75 c.c.), was treated with a solution of phenylmagnesium bromide [prepared from bromobenzene (46 c.c.) and magnesium (10·5 g.) in ether (150 c.c.)]; after 2 hours' refluxing the mixture was poured into ice-water and worked up in the usual way. The resultant oil was chromatographed on aluminium oxide (250 g.) prepared in pentane. Elution with pentane gave an oil consisting mainly of bromobenzene and diphenyl, whilst elution with benzene–pentane (1 : 1; 2 × 1 l.) gave 2-(3α-cholestanyl)-1 : 1-diphenylethanol as an oil (9·7 g.).

2-(3α-*Cholestanyl*)-1 : 1-*diphenylethylene*.—The above oil (9·7 g.), dissolved in pyridine (45 c.c.), was treated with thionyl chloride (10 c.c.) at 0° for 5 min. and then at 15° for 15 min. Dilution with ice-water, ether-extraction, and the usual working up gave an oil, which was dissolved in pentane and filtered through a column of aluminium oxide. Evaporation of the filtrate gave 2-(3α-*cholestanyl*)-1 : 1-*diphenylethylene* as plates (5·9 g.), m. p. 92°, $[\alpha]_D$ +64° (*c*, 0·91), from ethanol (Found, after sublimation at 160°/0·01 mm.: C, 89·4; H, 10·5. $C_{41}H_{58}$ requires C, 89·4; H, 10·6%).

Cholestane-3α-carboxylic Acid.—2-(3α-Cholestanyl)-1 : 1-diphenylethylene (2·3 g.), dissolved in purified chloroform (20 c.c.) and acetic acid (150 c.c.), was oxidised with a solution of chromium trioxide (2 g.) in 90% acetic acid at 15° for 2 hr. Excess of chromium trioxide was destroyed by addition of methanol, and solvents were removed in a vacuum. After addition of water and a little 2N-sulphuric acid, extraction with ether gave an ethereal solution from which no acid was extracted by 2N-potassium hydroxide. Evaporation of the dry ethereal solution gave an opaque solid, which afforded a precipitate when triturated with pentane. Collection of this potassium salt, acidification of its aqueous solution, and extraction with ether gave *cholestane-3α-carboxylic acid* (760 mg.), m. p. 163°, $[\alpha]_D$ +24° (*c*, 1·71), after crystallisation from 90% acetone (Found, after sublimation at 160°/0·01 mm.: C, 80·8; H, 11·4. $C_{24}H_{48}O_2$ requires C, 80·7; H, 11·6%). The *methyl ester*, prepared by ethereal diazomethane, formed prisms, m. p. 92°, $[\alpha]_D$ +27° (*c*, 3·1) (Found, after sublimation at 160°/0·01 mm.: C, 81·0; H, 11·7. $C_{30}H_{50}O_2$ requires C, 81·0; H, 11·7%).

We thank Glaxo Laboratories Ltd. for gifts of cholesterol; one of us (R. J. S.) gratefully acknowledges the receipt of a maintenance grant from the Department of Scientific and Industrial Research.

Department of Chemistry, University College,
Singleton Park, Swansea.

[*Received, October 15th*, 1953.]

Aromatic Azo-Compounds. Part VI. The Action of Light on Azoxy-Compounds.*

By G. M. Badger and R. G. Buttery.

[Reprint Order No. 5126.]

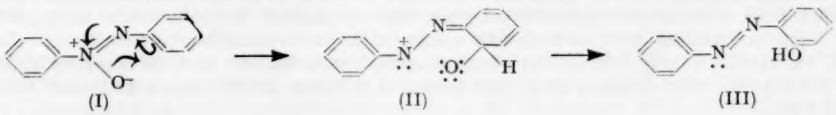
A number of azoxy-derivatives have been isomerised to *o*-hydroxyazo-derivatives by exposure to sunlight, the oxygen atom migrating from nitrogen to the further nucleus. An intramolecular mechanism is therefore proposed. The supposed red " isomers " of the azoxynaphthalenes are mixtures.

Cumming and Steel (*J.*, **1923**, **123**, 2464) reported that exposure of yellow 1 : 1′-azoxynaphthalene to sunlight or ultra-violet light rapidly converted it into a red form. A similar change was claimed for 2 : 2′-azoxynaphthalene (Cumming and Ferrier, *J.*, 1924, **125**, 1108). In each case the two forms had identical or almost identical melting points, and it was suggested that they were structural isomers. On the other hand, many azoxy-compounds (including 1 : 1′-azoxynaphthalene) are known to be converted into *o*-hydroxyazo-compounds by *prolonged* exposure to light (Cumming and Ferrier, *J.*, 1925, **127**, 2374; Cumming and Howie, *J.*, 1931, 3181). The interpretation put forward by Cumming *et al.* is not in accord with the modern view that azoxy-compounds contain a co-ordinate covalent bond [R·N(→O):N·R′], so these changes have been reinvestigated.

By using chromatography we have shown that the red " isomer " of 1 : 1′-azoxynaphthalene is a mixture of unchanged material with 2-hydroxy-1 : 1′-azonaphthalene, $C_{10}H_7·N:N·C_{10}H_6·OH$, in agreement with Cumming and Howie's conclusion (*loc. cit.*) that this naphthol is formed by the prolonged exposure of 1 : 1′-azoxynaphthalene to light. Similarly, the red " isomer " of 2 : 2′-azonaphthalene is a mixture of unchanged material and of 1-hydroxy-2 : 2′-azonaphthalene.

This rearrangement of azoxy-derivatives by light is formally similar to the Wallach transformation by sulphuric acid (see Gore and Hughes, *Austral. J. Sci. Res.*, 1950, **3**, *A*, 136); but the acid-catalysed rearrangement of azoxybenzenes gives derivatives of 4-hydroxyazobenzene with smaller quantities of 2-hydroxyazobenzenes and other products, whereas the light-catalysed isomerisation seems to lead exclusively, or almost exclusively, to 2-hydroxy-derivatives.

To establish whether the oxygen atom migrates from the nitrogen atom to the adjacent or the non-adjacent aromatic ring, some unsymmetrical azo-compounds have been investigated. α-2-Phenylazoxynaphthalene, $Ph·N(→O):N·C_{10}H_7$, gave 1-hydroxy-2-phenylazonaphthalene on exposure to light; the β-isomer, $Ph·N:N(→O)·C_{10}H_7$, was partly converted into 2-*o*-hydroxyphenylazonaphthalene. Similarly, β-1-phenylazoxynaphthalene gave 2-hydroxy-1-phenylazonaphthalene. Again, α-4-bromoazoxybenzene, $Ph·N(→O):N·C_6H_4Br$, gave 4-bromo-2-hydroxyazobenzene, and the β-isomer gave 4-bromo-2′-hydroxyazobenzene. In all these cases, therefore, the oxygen migrates from the nitrogen atom to which it is attached to the nucleus which is attached to the other nitrogen atom. As the $-N=$ valency angle is 120°, the *ortho*-position of the nucleus affected is closer in space to the oxygen atom than is the *ortho*-position of the other nucleus (cf. I).



(I) (II) (III)

This, together with the fact that *o*-hydroxy-derivatives appear to be formed exclusively, indicates that an intramolecular mechanism is probably involved and the scheme (I) ⟶ (III) is tentatively suggested.

That α-2-phenylazoxynaphthalene gives the 1-hydroxy-derivative exclusively, is in agreement with this mechanism, for the quinonoid transition state (as II), leading to

* Part V, *J.*, 1954, 1888.

substitution in the 1-position, would be much more stable than that leading to substitution in the 3-position (cf. naphtha-1 : 2- and -2 : 3-quinone).

In several cases the solvent had a marked effect on the rate of the rearrangement: migration was extremely slow in light petroleum, slow in benzene, and relatively rapid in ethanol. The yields also varied with the time of exposure, but were generally about 5—15% for 1 month's irradiation.

The azoxy-derivatives were prepared by peracetic acid oxidation of the azo-compounds. 2-Phenylazonaphthalene gave a mixture of the isomers, which were separated by fractional crystallisation from light petroleum (cf. Badger and Lewis, *J.*, 1953, 2151). 4-Bromoazobenzene also gave a mixture; fractional crystallisation from light petroleum gave the two isomers, the structures of which have been established by Angeli and Valori (*Atti R. Accad. Lincei*, 1912, **21**, I, 155). 1-Hydroxy-2 : 2′-azonaphthalene was prepared, in poor yield, from 1 : 2-naphthaquinone and 2-naphthylhydrazine. For the preparation of 2-*o*-hydroxyphenylazonaphthalene, *o*-nitroanisole was condensed with 2-naphthylamine in the presence of sodium hydroxide (cf. Martynoff, *Compt. rend.*, 1946, **223**, 747), and the product demethylated; 4-bromo-2′-hydroxyazobenzene was prepared similarly (cf. Martynoff, *loc. cit.*).

Experimental

Irradiations.—(a) 1 : 1′-*Azoxynaphthalene.* A benzene solution of 1 : 1′-azoxynaphthalene (m. p. 127°) was exposed to sunlight for 1 month. The resulting red solution was chromatographed on alumina whereby it was separated into unchanged material and 2-hydroxy-1 : 1′-azonaphthalene. After recrystallisation from alcohol the latter had m. p. 229° alone or admixed with an authentic specimen prepared according to Meldola and Hanes (*J.*, 1894, **65**, 834). The specimens had identical spectra with maxima at 5100 (log ε 4·31) and 4440 Å (log ε 4·10), and points of inflexion at 3200 (log ε 3·91) and 2720 Å (log ε 4·16).

The supposed red "isomer" of 1 : 1′-azoxynaphthalene was also prepared according to Cumming and Steel (*loc. cit.*) by allowing its solution in chloroform to evaporate in sunlight. The red solid obtained had m. p. 127°, not depressed by admixture with yellow 1 : 1′-azoxynaphthalene. Chromatography on alumina gave unchanged azoxynaphthalene and 2-hydroxy-1 : 1′-azonaphthalene.

(b) 2 : 2′-*Azoxynaphthalene.* A chloroform solution of 2 : 2′-azoxynaphthalene (m. p. 166°) was irradiated by sunlight for 1 month. After removal of the chloroform the product was chromatographed in benzene on alumina. Unchanged 2 : 2′-azoxynaphthalene was isolated, together with 1-*hydroxy*-2 : 2′-*azonaphthalene*, red-brown needles, m. p. 168° (from ethanol) (Found: C, 80·6; H, 4·7; N, 9·5. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7; N, 9·4%). The m. p. was not depressed by admixture with a specimen prepared as described below, and the specimens had identical spectra with maxima at 5080 (log ε 4·32), 3520 (log ε 4·14), and 2980 Å (log ε 4·36).

The supposed red "isomer" of 2 : 2′-azoxynaphthalene was also prepared as described by Cumming and Ferrier (*loc. cit.*) by exposing a saturated ethanolic solution to sunlight. The red crystals obtained had m. p. 164°, and when mixed with the original material had m. p. 165°. Chromatography of a benzene solution of the red "isomer" gave unchanged 2 : 2′-azoxynaphthalene and 1-hydroxy-2 - 2′-azonaphthalene.

(c) β-1-*Phenylazoxynaphthalene.* A benzene solution was exposed to sunlight for 1 month and then chromatographed on alumina. Elution of the red band and recrystallisation of the product from ethanol gave 2-hydroxy-1-phenylazonaphthalene as red needles, m. p. 133—134° alone or admixed with an authentic specimen prepared according to Liebermann (*Ber.*, 1883, **16**, 2858). The specimens had identical spectra with maxima at 4780 (log ε 4·17), 3120 (log ε 3·86), and 2300 Å (log ε 4·56), and points of inflexion at 2600 (log ε 4·02) and 4200 Å (log ε 4·01).

(d) α-2-*Phenylazoxynaphthalene.* This was irradiated in benzene solution for 1 month and then chromatographed. Elution of the red band and recrystallisation from ethanol gave 1-hydroxy-2-phenylazonaphthalene as red needles, m. p. 137° alone or mixed with a specimen prepared according to Zincke and Bindewald (*Ber.*, 1884, **17**, 3026). The specimens had identical spectra with maxima at 4900 (log ε 4·12), 3560 (log ε 3·92), and 2940 Å (log ε 4·12).

(e) β-2-*Phenylazoxynaphthalene.* Irradiation and chromatography, as for the isomer, gave 2-*o*-hydroxyphenylazonaphthalene as orange needles, m. p. 125° (from ethanol) alone or

mixed with a specimen prepared as described below. The specimens had identical spectra with maxima at 3940 (log ε 4·21), 3330 (log ε 4·36), and 2940 Å (log ε 4·12), and a point of inflexion at 2840 Å (log ε 4·06).

(f) α-4-*Bromoazoxybenzene*. An ethanolic solution was exposed to sunlight for 1 month. After removal of the ethanol the product was dissolved in equal quantities of benzene and light petroleum (b. p. 40—100°), and the solution chromatographed. 4-*Bromo*-2-*hydroxyazobenzene* separated from ethanol as red needles, m. p. 136—137° (Found: C, 51·95; H, 3·4; N, 10·1. $C_{12}H_9ON_2Br$ requires C, 52·0; H, 3·3; N, 10·1%). It was identified by comparison of its methyl ether with an authentic specimen prepared as below.

(g) β-4-*Bromoazoxybenzene*. The isomerisation and purification were carried out as for the α-compound. 4-Bromo-2′-hydroxyazobenzene separated from ethanol as orange-yellow needles, m. p. 133° alone or mixed with an authentic specimen prepared as described below. The specimens also had identical spectra with maxima at 3800 (log ε 4·06), 3320 (log ε 4·32), and 2440 Å (log ε 4·00).

Preparations.—1-*Hydroxy*-2 : 2′-*azonaphthalene*. A solution of 2-naphthylhydrazine hydrochloride (2 g.) in glacial acetic acid (100 c.c.) was added to one of naphtha-1 : 2-quinone (1·6 g.) in glacial acetic acid (100 c.c.), and the mixture kept at room temperature for 2 days. Water was added and the precipitated solid was collected, dried, and extracted with benzene. Chromatography on alumina gave a bright red band and a considerable quantity of strongly adsorbed tarry material. Elution of the red band gave 1-hydroxy-2 : 2′-azonaphthalene (0·2 g.) identical with the specimen described above.

2-o-*Hydroxyphenylazonaphthalene*. *o*-Nitroanisole (50 g.) and 2-naphthylamine (100 g.) were heated to 170—180°, and powdered sodium hydroxide (36 g.) added during 30 min. The reaction was strongly exothermic and cooling at times was necessary. After a further 30 minutes' stirring the mixture was cooled and the product washed with 6N-hydrochloric acid, dried, and then extracted with equal quantities of benzene and light petroleum (b. p. 40—100°). The resulting solution was chromatographed on alumina. The most weakly adsorbed band was eluted, the solvent evaporated, and the product recrystallised from ethanol. 2-o-*Methoxyphenylazonaphthalene* was obtained as orange needles (10 g.), m. p. 92·5° (Found: C, 77·9; H, 5·4; N, 10·9. $C_{17}H_{14}ON_2$ requires C, 77·9; H, 5·4; N, 10·7%). Demethylation was effected by an equal weight of aluminium chloride in boiling benzene, for 7 min. After decomposition with water and purification by chromatography and recrystallisation, 2-o-*hydroxyphenylazonaphthalene* was obtained as orange needles, m. p. 125° (Found: C, 77·5; H, 4·9; N, 11·25. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9; N, 11·3%).

4-*Bromo*-2-*methoxyazobenzene*. 4-Amino-2-methoxyazobenzene (10 g.; Earl and Robson, *J. Proc. Austral. Chem. Inst.*, 1939, **6**, 268) was stirred into hydrobromic acid (*d* 1·46; 25 c.c.) and water (200 c.c.). After cooling to 5°, sodium nitrite (3·5 g.) in a little water was added gradually with stirring. After a further 15 minutes' stirring the solution was added slowly at 60° to one of cuprous bromide [prepared by refluxing copper sulphate (6 g.), copper turnings (10 g.), potassium bromide (18 g.), concentrated sulphuric acid (5 g.), and water (40 c.c.)]. The brown solid which was precipitated was purified by chromatography and recrystallisation from ethanol. 4-*Bromo*-2-*methoxyazobenzene* (3 g.) was obtained as orange needles, m. p. 76·5° (Found: C, 53·9; H, 3·9; N, 9·8. $C_{13}H_{11}ON_2Br$ requires C, 53·6; H, 3·8; N, 9·6%). The m. p. was not depressed by admixture with a specimen prepared by methylation of the above 4-bromo-2-hydroxyazobenzene with methyl sulphate. The specimens had identical spectra with maxima at 4360 (log ε 3·18), 3560 (log ε 4·11), and 3200 Å (log ε 4·07).

4-*Bromo*-2′-*hydroxyazobenzene*. *o*-Nitroanisole (30 g.) and *p*-bromoaniline (60 g.) were heated to 170—180° and powdered sodium hydroxide (22 g.) added with stirring during 30 min. Stirring was continued for a further 30 min. at the same temperature, with cooling when necessary. The cold solid was washed with 6N-hydrochloric acid, dried, dissolved in a mixture of equal parts of benzene and light petroleum (b. p. 40—100°), and chromatographed. The least adsorbed band was eluted and the solvent evaporated. 4-*Bromo*-2′-*methoxyazobenzene* (30 g.) separated from ethanol as orange needles, m. p. 83° (Found: C, 53·8; H, 3·8; N, 9·6%). It was demethylated as above to 4-*bromo*-2′-*hydroxyazobenzene*, orange-yellow needles, m. p. 133° (Found: C, 52·25; H, 3·4; N, 9·8. $C_{12}H_9ON_2Br$ requires C, 52·0; H, 3·3; N, 10·1%), identical with the specimen described above.

Microanalyses were carried out at the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, February 15th*, 1954.]

The Aporphine Series. Part I. Developments of the Bischler–Napieralski–Pschorr Synthetic Method. The Synthesis of (±)-iso*Bulbocapnine and* (±)-*Actinodaphnine Methyl Ether.*

By D. H. Hey and L. C. Lobo.

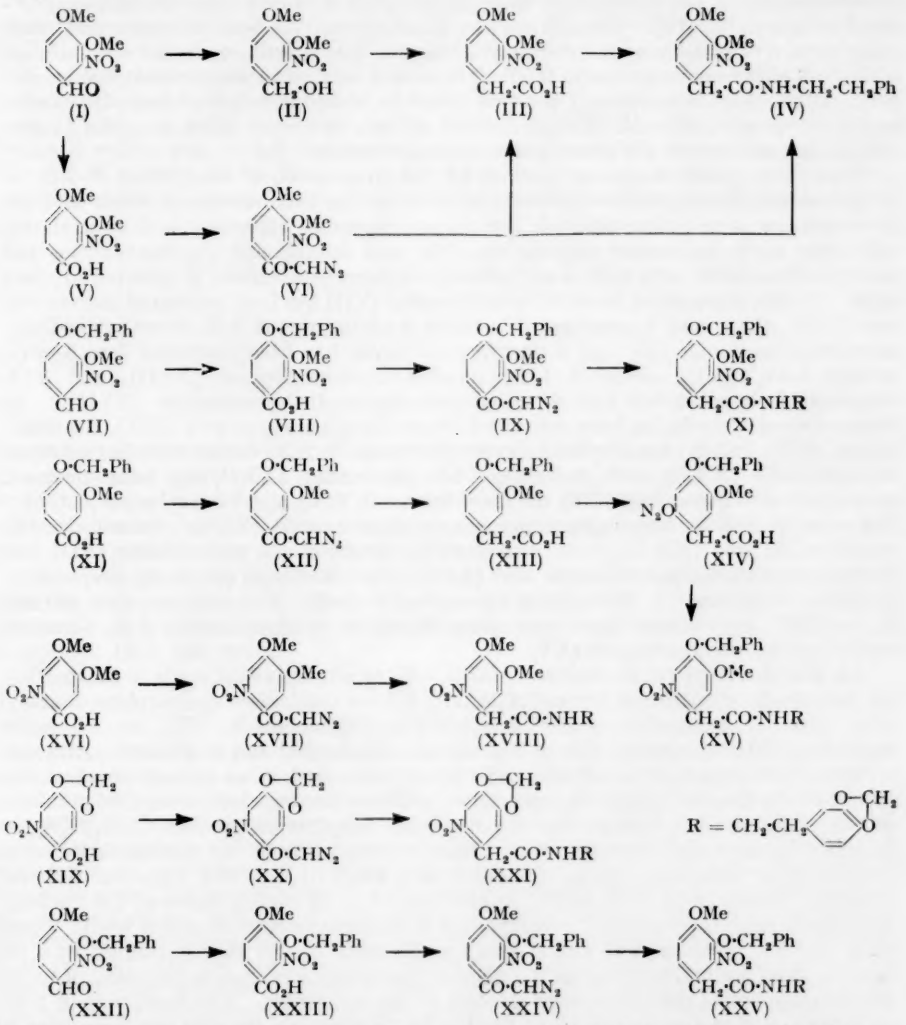
[Reprint Order No. 4897.]

An improved method has been developed for the synthesis of *N*-2-arylethyl-*o*-nitroarylacetamides which is illustrated by the preparation of seven members of this class. Contrary to the claim of Späth and Hromatka, and in agreement with the earlier work of Kay and Pictet, Kondo, and Gulland, Haworth, Virden, and Callow, it has not been possible to convert 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide into a derivative of *iso*quinoline by means of the Bischler–Napieralski reaction. On the other hand, four substituted *N*-2-(3 : 4-methylenedioxyphenyl)ethyl-*o*-nitrophenylacetamides have been converted by means of the successive application of the Bischler–Napieralski and the Pschorr reaction into derivatives of aporphine or noraporphine. In two examples in the aporphine series, in which the benzyl group is used as a protective group, this method has led to the first syntheses of members of the hydroxyaporphine series. The compounds synthesised include (±)-*iso*bulbocapnine and (±)-actinodaphnine methyl ether.

Apart from the synthesis of several aporphine ethers there are few groups of alkaloids in which synthetic work is less satisfactory than in the aporphine group. *apo*Morphine (3 : 4-dihydroxyaporphine) and its dimethyl ether (*apo*-ψ-codeine) have long been recognised as dehydration and rearrangement products of morphine and codeine respectively. Although the constitution of these compounds has been established by degradation, *apo*morphine has never been synthesised and considerable doubt exists concerning the claims for the synthesis of *apo*morphine dimethyl ether made by both Avenarius and Pschorr (*Ber.*, 1929, **62**, 321) and Späth and Hromatka (*ibid.*, p. 325). The validity of the former synthesis was questioned by Gulland and Virden (*J.*, 1929, 1794), and in a later communication (*Chem. and Ind.*, 1938, **16**, 774) Gulland pointed out that the product prepared by Avenarius and Pschorr was not a derivative of *apo*morphine but rather a derivative of tetrahydro-2-methyl*iso*quinoline. Doubt also surrounds the claims of Späth and Hromatka because their method had previously been tried without success by Kay and Pictet (*J.*, 1913, **103**, 947), Kondo (*J. Pharm. Soc., Japan*, 1925, 429), and Gulland, Haworth, Virden, and Callow (*J.*, 1929, 1666). In addition, the identity of the products from the synthetic and the natural source was established with a scission product, and the key intermediate used in this method, namely, 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV), was reported to melt at 98° by Kay and Pictet, at 119° by Kondo, and at 79° and 117° by Späth and Hromatka. Further, although many attempts have been made to synthesise phenolic aporphines, notably by Gulland and his co-workers (*J.*, 1931, 2872, 2881, 2885, 2893), little success attended their efforts. These workers carried out preliminary work with both the benzyl and the ethoxycarbonyl group as protecting groups which could subsequently be removed but the completion of this work, including the description of one phenolic aporphine, has not been published. There is thus no record of an authentic synthesis of a hydroxyaporphine, although Kondo and Ishiwata (*Ber.*, 1931, **64**, 1533) reported the synthesis of 6-hydroxy-3 : 4-dimethoxynoraporphine.

It is thus clear that certain aspects of the synthetic work in the aporphine series require further investigation, and with the knowledge now available on the Bischler–Napieralski reaction (see Whaley and Govindachari, *Organic Reactions*, 1951, **6**, 74), on the Pschorr reaction (Hey and Osbond, *J.*, 1949, 3164 and following papers), and on the use of protective groups for phenolic compounds, it would seem that the time is opportune for attacking some of these problems afresh. The present communication is concerned with

the classical synthetic method which involves (*a*) the preparation of a substituted *o*-nitrophenyl-*N*-phenethylacetamide, (*b*) conversion into a 3 : 4-dihydro*iso*quinoline by means of the Bischler–Napieralski reaction, (*c*) methylation and reduction to give a substituted 1-*o*-aminobenzyltetrahydro-2-methyl*iso*quinoline, and finally (*d*) ring closure to the aporphine structure by means of the Pschorr reaction.



The Preparation of the Amides.—The preparation of 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV) has been claimed by several authors. The first synthesis was effected by a ten-stage process from vanillin and the amide was stated to melt at 98° (Kay and Pictet, *loc. cit.*). Later preparations were carried out by Kondo (*loc. cit.*), who reported m. p. 119°, and Späth and Hromatka (*loc. cit.*), who reported the existence of two forms, m. p. 79° and 117°. Two methods of preparation are now described and both lead to a product of m. p. 79°. The first method is based on that of Kay and Pictet (*loc. cit.*) and involves the intermediates (I), (II), and (III) but improvements, reported in

detail in the Experimental section, have been effected at several stages. This improved method was found, in our hands, to be superior to the somewhat similar method described by Slotta and Lauerson (*J. pr. Chem.*, 1934, **139**, 220) for the preparation of 2-nitrohomoveratric acid (III). In the second method 2-nitroveratraldehyde (I) was oxidised to 2-nitroveratric acid (V) by the action of silver oxide, and the acid was converted successively into the acid chloride and the diazo-ketone (VI). The latter, on treatment with phenethylamine in the presence of silver oxide, gave 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV). In addition, the diazo-ketone (VI) with ammonia and silver oxide gave 3 : 4-dimethoxy-2-nitrophenylacetamide, which was converted with nitrous acid into 2-nitrohomoveratric acid (III). The second method of preparation gave inferior yields, although a comparison of the two routes to *o*-nitrophenyl-*N*-phenethylacetamide from *o*-nitrophenylacetic acid through the acid chloride on the one hand, and from *o*-nitro-ω-diazoacetophenone on the other, gave comparable yields.

From these results a general method for the preparation of substituted *N*-2-(3 : 4-methylenedioxyphenyl)ethyl-*o*-nitrophenylacetamides has been developed which involves the conversion of an *o*-nitro-aldehyde into the corresponding carboxylic acid by oxidation with silver oxide, subsequent preparation of the acid chloride and the diazo-ketone, and reaction of the latter with 2-(3 : 4-methylenedioxyphenyl)ethylamine in presence of silver oxide. In this manner, (*a*) 2-nitro-*O*-benzylvanillin (VII) has been converted successively into (VIII), (IX), and 4-benzyloxy-3-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (X); (*b*) 6-nitroveratraldehyde has been converted into 6-nitroveratric acid (XVI), ω-diazo-3 : 4-dimethoxy-6-nitroacetophenone (XVII), and 3 : 4-dimethoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XVIII); (*c*) 6-nitropiperonaldehyde has been converted into 6-nitropiperonylic acid (XIX), the diazo-ketone (XX), and 3 : 4-methylenedioxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)-ethylacetamide (XXI); and (*d*) 2-nitro-*O*-benzyl*iso*vanillin (XXII) has been converted successively into the acid (XXIII), the diazo-ketone (XXIV), and 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XXV). In addition, *O*-benzylvanillic acid (XI) has been converted by means of the diazo-ketone (XII) into 4-benzyloxy-3-methoxyphenylacetic acid (XIII), which had been previously prepared by Douglas and Gulland (*J.*, 1931, 2893) by another method. This acid was then nitrated to give (XIV) and converted into 4-benzyloxy-3-methoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XV).

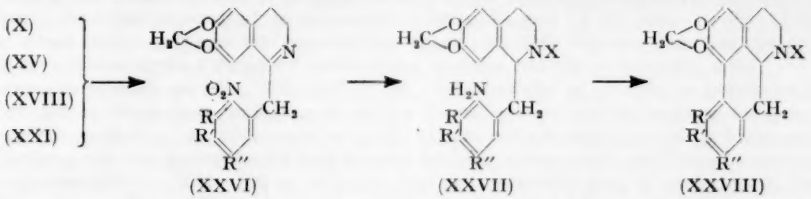
The Bischler–Napieralski–Pschorr Reaction.—Many attempts were made to substantiate the claim made by Späth and Hromatka (*loc. cit.*) to have synthesised apomorphine dimethyl ether from 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (IV) by successive application of the procedures due to Bischler and Napieralski and to Pschorr. Although a variety of experimental conditions and reagents were used in an attempt to effect ring closure to the dihydro*iso*quinoline no positive evidence for ring closure could be obtained, and the only product isolated was the non-basic dehydration product $C_{18}H_{18}O_4N_2$, as described by Kay and Pictet (*loc. cit.*). These results, as far as the non-formation of an *iso*quinoline is concerned, are in agreement with those of Kay and Pictet, of Gulland, Haworth, Virden, and Callow, and of Kondo (*locc. cit.*). A similar failure at the Bischler–Napieralski stage occurred with *o*-nitrophenyl-*N*-phenethylacetamide and it would appear likely that the presence of an *o*-nitro-group in the phenylacetyl moiety, coupled with the absence of an activating group in the phenethylamino-moiety, makes ring closure to the dihydro*iso*quinoline derivative very difficult, if not impossible. The usefulness of polyphosphoric acid as a reagent to effect the Bischler–Napieralski reaction was demonstrated by the formation of 1-benzyl-3 : 4-dihydro*iso*quinoline from *N*-phenethylphenylacetamide.

The successful conversion of a series of *N*-2-(3 : 4-methylenedioxyphenyl)ethyl-*o*-nitrophenylacetamides into derivatives of aporphine or noraporphine has been achieved in the following four examples.

4-Benzyloxy-3-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (X) was converted into 1-(4-benzyloxy-3-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline (XXVI; R = MeO, R′ = Ph·CH_2·O, R″ = H) by the action of phosphorus pentachloride in chloroform. The base was converted into the

methiodide, which was then reduced with zinc and hydrochloric acid to 1-(2-amino-4-benzyloxy-3-methoxylbenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline (XXVII; R = MeO, R′ = Ph·CH_2·O, R″ = H, X = Me). Diazotisation of this base with barium nitrite, decomposition with the addition of copper powder, and subsequent debenzylation gave (±)-3-hydroxy-4-methoxy-5 : 6-methylenedioxyaporphine (XXVIII; R = MeO, R′ = HO, R″ = H, X = Me), also known as *iso*bulbocapnine.

In similar manner 4-benzyloxy-3-methoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XV) gave (XXVI; R = H, R′ = Ph·CH_2·O, R″ = MeO), (XXVII; R = H, R′ = Ph·CH_2·O, R″ = MeO, X = Me), and (±)-3-hydroxy-2-methoxy-5 : 6-methylenedioxyaporphine (XXVIII; R = H, R′ = HO, R″ = MeO, X = Me); 3 : 4-dimethoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XVIII) gave (XXVI; R = H, R′ = MeO, R″ = MeO), (XXVII; R = H, R′ = MeO, R″ = MeO, X = H), and (±)-2 : 3-dimethoxy-5 : 6-methylenedioxynoraporphine (XXVIII; R = H, R′ = MeO, R″ = MeO, X = H), which is (±)-actinodaphnine methyl ether; and 3 : 4-methylenedioxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide



(XXI) gave (XXVI; R = H, R′R″ = ·O·CH_2·O·), (XXVII; R = H, R′R″ = ·O·CH_2·O·, X = Me), and (±)-2 : 3-5 : 6-bismethylenedioxyaporphine (XXVIII; R = H, R′R″ = ·O·CH_2·O·, X = Me). Preliminary attempts to effect ring closure with 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (XXV) and phosphorus pentachloride resulted in debenzylation.

The above examples include the synthesis of two phenolic aporphines, one aporphine ether, and one noraporphine ether. The aporphine ether which corresponds with the last-named compound, namely (±)-dicentrine, was synthesised by Haworth, Perkin, and Rankin (*J.*, 1925, **127**, 2022).

Experimental

Preparation of amides.

3 : 4-*Dimethoxy*-2-*nitrophenyl*-N-*phenethylacetamide* (IV).—*Method* (*a*). *O*-Acetylvanillin was nitrated by Pschorr and Sumuleanu's method (*Ber.*, 1899, **32**, 3405), but at −12° to −20°, to give in 80% yield *O*-acetyl-2-nitrovanillin, which was hydrolysed by boiling with dilute hydrochloric acid for 2 hr. 2-Nitrovanillin separated in yellow needles, m. p. 137°, in 80% overall yield. To an ice-cold solution of 2-nitrovanillin (50 g.) in methyl alcohol (100 c.c.) and methyl sulphate (63 g.) was added 30% aqueous sodium hydroxide (75 c.c.) dropwise with stirring. The mixture was then heated to the b. p. and methyl sulphate (20 g.) was added followed by 30% aqueous sodium hydroxide (20 c.c.). This procedure was repeated twice. On cooling, 2-nitroveratraldehyde separated, which crystallised from alcohol in pale yellow needles (46·5 g.), m. p. 54—56°. For the conversion of 2-nitroveratraldehyde into 3 : 4-dimethoxy-2-nitrobenzyl alcohol the following methods proved superior to that of Kay and Pictet (*loc. cit.*): (i) A solution of 2-nitroveratraldehyde (10 g.) in dry *iso*propyl alcohol (200 c.c.), added to a solution of aluminium *iso*propoxide (5 g.) in *iso*propyl alcohol (50 c.c.), was distilled at the rate of 2—3 drops a minute, the total volume of the solution being kept constant until the distillate was free from acetone (36 hr.). Excess of *iso*propyl alcohol was removed by distillation and the residue warmed to 50° with 10% sulphuric acid. 3 : 4-Dimethoxy-2-nitrobenzyl alcohol (7·5 g.) was collected and crystallised from alcohol in yellow needles, m. p. 66—68°. (ii) (cf. Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905.) A solution of 2-nitroveratraldehyde (20 g.) in methyl alcohol (100 c.c.) and 40% formaldehyde solution (10 c.c.) was heated to 70° and 50% aqueous sodium hydroxide (15 c.c.) was added at such a rate that the temperature did not exceed 75°. After being boiled under reflux for 1 hr., the mixture was cooled and water

(100 c.c.) was added. The 3 : 4-dimethoxy-2-nitrobenzyl alcohol (16 g.) which separated crystallised from alcohol in yellow needles, m. p. 66—68°. Acidification of the filtrate gave 2-nitroveratric acid (0·7 g.), m. p. 200—202°. The alcohol (10 g.) was added in small portions to thionyl chloride (20 g.), cooled in ice. When the initial vigorous reaction had ceased, the solution was boiled under reflux for ½ hr., cooled, and poured on ice (200 g.). The 3 : 4-dimethoxy-2-nitrobenzyl chloride was collected, dried, and dissolved in benzene (15 c.c.). Addition of light petroleum (b. p. 60—80°) precipitated 3 : 4-dimethoxy-2-nitrobenzyl chloride (9 g.) in needles, m. p. 57—58°, which was converted into 3 : 4-dimethoxy-2-nitrobenzyl cyanide (7·5 g.), m. p. 68—69°, by boiling it in alcohol (170 c.c.) with aqueous potassium cyanide (18 g. in 15 c.c.) (cf. Kay and Pictet, *loc. cit.*). The cyanide (15 g.) was converted into 2-nitrohomoveratric acid (10 g.), m. p. 146°, and thence through the acid chloride into 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (10 g.), white needles, m. p. 79° (from alcohol) (Found : C, 62·6; H, 5·8; N, 8·0. Calc. for $C_{18}H_{20}O_5N_2$: C, 62·8; H, 5·8; N, 8·1%), as described by Kay and Pictet, who recorded m. p. 98° (from toluene) for this compound. Späth and Hromatka (*loc. cit.*) have recorded m. p. 79°.

Method (*b*). 2-Nitroveratraldehyde, prepared as in method (*a*), was oxidised to 2-nitroveratric acid by the following method, which is much superior to that of Pschorr and Sumuleanu (*loc. cit.*). Silver oxide (15 g.) was added to a suspension of 2-nitroveratraldehyde (10 g.) in 2% aqueous sodium hydroxide (200 c.c.) at 70° and the mixture was then boiled under reflux for 4 hr. After filtration of the hot solution acidification liberated 2-nitroveratric acid (9 g.), which separated on cooling in yellow leaflets, m. p. 201—202°. In an alternative procedure 15% aqueous sodium hydroxide was slowly added to a boiling suspension of 2-nitroveratraldehyde (10 g.) in a solution of silver nitrate (16 g.) in water (200 c.c.). Boiling under reflux was continued until the silver mirror initially formed had disintegrated and the product was worked up as before, to give 2-nitroveratric acid (9 g.), m. p. 201—202°. 2-Nitroveratric acid (10 g.) was converted into 2-nitroveratroyl chloride (9 g.), m. p. 73°, by Pisovschi's method (*Ber.*, 1910, **43**, 2141). A solution of the acid chloride (9 g.) in dry benzene (20 c.c.) was added to ethereal diazomethane, prepared from nitrosomethylurea (20 g.), at 0—5°. After 3 hr. the *ω-diazo-3 : 4-dimethoxy-2-nitroacetophenone* (8 g.), which separated, was collected and crystallised from dry benzene, giving very pale yellow needles, m. p. 116° (decomp.) (Found : C, 48·1; H, 3·7. $C_{10}H_9O_5N_3$ requires C, 47·8; H, 3·6%). Phenethylamine (3 g.) and silver oxide (0·5 g.) were added to a solution of the diazo-ketone (5 g.) in dry benzene (100 c.c.) at 60°. Evolution of nitrogen was slow and after 10 min. alcohol (1 c.c.) was added and the temperature was kept at 65—70° for 2 hr. After filtration light petroleum (b. p. 60—80°) was added to the cooled filtrate until a small quantity of a dark oil began to separate. The clear solution was decanted from the oil and the operation was repeated with the addition of more light petroleum. The solution which was then considerably paler was diluted with an excess of light petroleum (b. p. 60—80°), which precipitated a red oil which solidified at 0°. The solid product was dissolved in alcohol, to which water was added until a slight turbidity appeared. After the addition of charcoal the mixture was boiled under reflux and filtered. The yellow filtrate, on cooling, deposited an oil which solidified (2 g.; m. p. 62—67°). Three recrystallisations from alcohol gave 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (0·5 g.) in white needles, m. p. 79°, undepressed on admixture with the product prepared by method (*a*) above.

To a portion of the diazo-ketone (1 g.) in dioxan (15 c.c.) were added a solution of ammonia (*d* 0·880; 5 c.c.) in water (5 c.c.) and then silver oxide (0·2 g.) and alcohol (0·5 c.c.). The mixture was kept at 50° for 1 hr. Nitrogen was evolved and after being boiled under reflux for ½ hr. the mixture was filtered. Water was added to the filtrate (until turbidity was produced) and the whole was then boiled with charcoal and filtered. 3 : 4-Dimethoxy-2-nitrophenylacetamide (0·22 g.) which separated on cooling formed needles, m. p. 150—151°, from hot water (cf. Gulland and Virden, *J.*, 1929, 1803). When a solution of sodium nitrite (0·3 g.) in water (3 c.c.) was added slowly to a solution of the amide (1 g.) in concentrated sulphuric acid (5 c.c.), cooled in ice, nitrogen was liberated with evolution of heat. When the reaction had subsided water (25 c.c.) was added and the solution was boiled under reflux for 15 min. On cooling, 2-nitrohomoveratric acid (0·7 g.) separated, which crystallised from hot water in white leaflets, m. p. 144—146°, identical with the product obtained above from the hydrolysis of 3 : 4-dimethoxy-2-nitrobenzyl cyanide.

o-*Nitrophenyl*-N-*phenethylacetamide*.—*Method* (*a*). *o*-Nitrophenylacetic acid (10 g.) in dry benzene (20 c.c.) was boiled under reflux for 2 hr. with thionyl chloride (12 g.). Excess of thionyl chloride and benzene were removed under reduced pressure and the residual *o*-nitrophenylacetyl chloride was redissolved in benzene (30 c.c.) and added in small portions to

a suspension of phenethylamine (8 g.) in water (20 c.c.) cooled in ice. Aqueous sodium hydroxide (10%; 20 c.c.) was added, and after 15 min. the benzene layer was separated, washed with dilute hydrochloric acid, and dried. Addition of light petroleum (b. p. 60—80°) deposited *o*-nitrophenyl-*N*-phenethylacetamide (12 g.), which separated from aqueous alcohol in needles, m. p. 98—99° (cf. Kay and Pictet, *loc. cit.*).

Method (*b*). To a solution of ω-diazo-*o*-nitroacetophenone (13 g.) (Arndt, Eistert, and Partale, *Ber.*, 1927, **60**, 1366) in benzene (100 c.c.) were added phenethylamine (9 g.), silver oxide (0·5 g.), and alcohol (2 c.c.). After being kept for 1 hr. at 70° the mixture was boiled under reflux for ½ hr. and filtered. Light petroleum (b. p. 60—80°) was added to the brown filtrate until a small quantity of dark oil separated, and the clear solution was then decanted. Further addition of light petroleum precipitated a brown oil which solidified. Recrystallisation from benzene gave *o*-nitrophenyl-*N*-phenethylacetamide (10 g.) in pale yellow needles, m. p. 98—99°, identical with the product prepared by method (*a*) above.

4-*Benzyloxy*-3-*methoxy*-2-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (X).—A mixture of 2-nitrovanillin (10 g.), dioxan (40 c.c.), benzyl chloride (9 g.), potassium carbonate (5 g.), and water (7 c.c.) was boiled under reflux for 4 hr. and then poured into water (200 c.c.) and distilled with steam until the distillate was clear. The oil which separated on cooling solidified. Crystallisation from alcohol, after treatment with charcoal, gave O-*benzyl*-2-*nitrovanillin* (13 g.) in needles, m. p. 108—109° (Found: C, 62·6; H, 4·5; N, 4·7. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·5; N, 4·9%). A mixture of this (10 g.), sodium carbonate (4 g.), silver oxide (9 g.), and water (200 c.c.) was boiled under reflux for 4 hr. When cold, the mixture was filtered and the residue was boiled with water (200 c.c.) and filtered hot. On cooling, sodium *O*-benzyl-2-nitrovanillate separated in plates. This was collected and dissolved in boiling water. On acidification, O-*benzyl*-2-*nitrovanillic acid* (9 g.) separated, which crystallised from alcohol in needles, m. p. 183—184° (Found: C, 60·0; H, 4·5. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3%). A small quantity of *O*-benzyl-2-nitrovanillic acid was also recovered by acidification of the original filtrate. In an alternative procedure a mixture of 2-nitrovanillin (20 g.), silver nitrate (25 g.), and water (200 c.c.) was heated to 80° and 25% aqueous sodium hydroxide (50 c.c.) was added. Boiling under reflux was continued until the silver mirror initially formed was completely disintegrated (1—1½ hr.). The mixture was worked up as before and gave *O*-benzyl-2-nitrovanillic acid (18 g.), m. p. 183—184°. *O*-Benzyl-2-nitrovanillic acid (12 g.) was added in small portions to a suspension of phosphorus pentachloride (9 g.) in dry chloroform (30 c.c.), and the mixture was set aside for ½ hr. after the acid had dissolved. After filtration, the solvent was removed at 30° under reduced pressure and cold dry ether (20 c.c.) was added to the residue. The granular 4-benzyloxy-3-methoxy-2-nitrobenzoyl chloride (11 g.) was collected, washed with cold ether, and dried. After crystallisation from benzene it was obtained in needles, m. p. 108°. The acid chloride (15 g.) in dry benzene (50 c.c.) was added in portions, with shaking, to a solution of diazomethane in ether (prepared from 20 g. of nitrosomethylurea) at 5°. After 3 hr. the diazo-ketone was collected and dried by suction. Crystallisation from benzene gave 4-*benzyloxy*-ω-*diazo*-3-*methoxy*-2-*nitroacetophenone* (14 g.) in pale yellow needles, m. p. 152—154° (decomp.) (Found: C, 58·8; H, 4·0. $C_{16}H_{13}O_5N_3$ requires C, 58·7; H, 4·2%). 2-(3 : 4-Methylenedioxyphenyl)ethylamine (4·5 g.; prepared as described by Decker, *Annalen*, 1913, **395**, 291) and silver oxide (0·5 g.) were added to a solution of freshly prepared 4-benzyloxy-ω-diazo-3-methoxy-2-nitroacetophenone (8 g.) in benzene (200 c.c.) at 65°. Nitrogen was evolved gently at this temperature which should not be exceeded, and after 2 hr. a further quantity of silver oxide (0·5 g.) was added and the mixture was boiled under reflux for ½ hr. After filtration the solution was concentrated to small bulk, and light petroleum (b. p. 60—80°) was added to the cold solution until a small quantity of brown oil separated which solidified. Further light petroleum was then added to complete the separation. The solid was collected and dissolved in boiling glacial acetic acid (6 c.c.). After 2 hr. the solid which had separated was collected under suction, pressed free from mother-liquor, and washed with cold glacial acetic acid (3 c.c.). Several recrystallisations from aqueous alcohol (with charcoal) gave 4-*benzyloxy*-3-*methoxy*-2-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (4·7 g.) in needles, m. p. 123—124° (Found: C, 64·3; H, 5·0; N, 5·9. $C_{25}H_{24}O_7N_2$ requires C, 64·7; H, 5·2; N, 6·0%).

4-*Benzyloxy*-3-*methoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (XV).—To a vigorously boiling mixture of *O*-benzylvanillin (20 g.; Dickinson, Heilbron, and Irving, *J.*, 1927, 1895), silver nitrate (32 g.), and water (150 c.c.), 40% aqueous sodium hydroxide (50 c.c.) was slowly added. After being boiled under reflux for 1 hr. the mixture was filtered and the filtrate acidified. Recrystallisation of the separated solid from benzene gave O-*benzyl*-

vanillic acid (19 g.) in needles, m. p. 171—172° (Found: C, 69·4; H, 5·2. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%). This acid (12 g.) was converted into the acid chloride (11 g.), m. p. 65—66°, as described above for the preparation of *O*-benzyl-2-nitrovanillic acid except that the solvent was removed below 30°. The acid chloride (11 g.) was in turn converted by the method described above for the 2-nitro-compound into 4-*benzyloxy*-ω-*diazo*-3-*methoxyacetophenone* (10 g.), pale yellow needles, m. p. 98—99° (decomp.; from alcohol) (Found: C, 67·9; H, 4·8. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0%). Silver oxide (0·5 g.) was added to a solution of the diazo-ketone (10 g.) in dioxan (50 c.c.) and ammonia (*d* 0·880; 20 c.c.), and the mixture was heated at 80° for 2 hr., filtered, and poured into water (100 c.c.). Recrystallisation of the solid which separated gave 4-*benzyloxy*-3-*methoxyphenylacetamide* (8 g.), which separated from hot water in plates, m. p. 133—134° (Found: C, 70·6; H, 6·1. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3%). Hydrolysis of the amide (6 g.) with boiling 10% aqueous sodium hydroxide gave 4-benzyloxy-3-methoxyphenylacetic acid (5 g.), which separated from benzene in prisms, m. p. 114—116°. The m. p. was not depressed on admixture with a specimen of the acid (m. p. 115—116°) prepared from 4-benzyloxy-3-methoxyphenylpyruvic acid by Douglas and Gulland's method (*J.*, 1931, 2897). Nitration by Douglas and Gulland's method gave 4-benzyloxy-3-methoxy-6-nitrophenylacetic acid in needles, m. p. 222°. The crude acid (6 g.) was converted into the acid chloride, as described above for the preparation of 4-benzyloxy-3-methoxy-2-nitrobenzoyl chloride, which in turn was added to a solution of 2-(3 : 4-methylenedioxyphenyl)ethylamine (4 g.) in chloroform (30 c.c.) at 0°. After 10 min. 5% aqueous sodium hydroxide (40 c.c.) was added and finally chloroform (50 c.c.). The chloroform layer was washed with dilute hydrochloric acid and dried, and the solvent was removed. Crystallisation of the residue from ethylene dichloride and then from alcohol gave 4-*benzyloxy*-3-*methoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (5 g.) in needles, m. p. 195—197° (Found: C, 64·6; H, 5·0. $C_{25}H_{24}O_7N_2$ requires C, 64·8; H, 4·9%).

3 : 4-*Dimethoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (XVIII).—Veratraldehyde was converted into 6-nitroveratraldehyde by Pschorr and Sumuleanu's method (*Ber.*, 1899, **32**, 3412). A solution of sodium hydroxide (15 g.) in water (50 c.c.) was added slowly to a mixture of 6-nitroveratraldehyde (25 g.), silver nitrate (40 g.), and water (200 c.c.) boiling under reflux. After further boiling for 1½ hr. the mixture was filtered and to the filtrate acid was added until the solution was only just alkaline. This solution was heated with charcoal and filtered. Acidification of the hot filtrate precipitated 6-nitroveratric acid (20 g.), yellow leaflets, m. p. 186° (from hot water). Simonsen and Rau (*J.*, 1918, **113**, 26) record m. p. 185—187°. 6-Nitroveratric acid (15 g.) was converted into the acid chloride (14·5 g.), m. p. 120—122°, by the method described above for *O*-benzyl-2-nitrovanillic acid. From the acid chloride (13 g.) in dioxan (40 c.c.) and ethereal diazomethane (200 c.c.), prepared from nitrosomethylurea (25 g.), at 0—5°, there was obtained ω-diazo-3 : 4-dimethoxy-6-nitroacetophenone (11·5 g.), in yellow needles, m. p. 157—158° (decomp.; from dioxan), which was too unstable for analysis. 2-(3 : 4-Methylenedioxyphenyl)ethylamine (7 g.) and silver oxide (0·5 g.) were added to a solution of the diazo-ketone (10·5 g.) in dioxan (150 c.c.) at 60°. Nitrogen was evolved and after 2 hr. more silver oxide (0·5 g.) was added and the temperature was raised to 100° for 10 min. After filtration the filtrate was cooled to 0° and the solid which separated was collected and washed with ice-cold methyl alcohol. Recrystallisation from ethylene dichloride gave 3 : 4-*dimethoxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (9·5 g.) in plates, m. p. 199—201° (Found: C, 58·1; H, 5·1; N, 6·8. $C_{19}H_{20}O_7N_2$ requires C, 58·8; H, 5·2; N, 7·2%).

3 : 4-*Methylenedioxy*-6-*nitrophenyl*-N-2-(3 : 4-*methylenedioxyphenyl*)*ethylacetamide* (XXI).—6-Nitropiperonaldehyde (10 g.) (Salway, *J.*, 1909, **95**, 1163) in 5% aqueous sodium carbonate (200 c.c.) was warmed to 70° and silver oxide (15 g.) added. The mixture was boiled under reflux until the purple colour changed to orange (1 hr.). After filtration and treatment with charcoal, acidification precipitated 6-nitropiperonylic acid, which separated from hot water in yellow plates (5 g.), m. p. 170—172° (cf. Jobst and Hesse, *Annalen*, 1879, **199**, 70). In an alternative preparation piperonaldehyde (30 g.) was oxidised with silver nitrate in alkaline solution, as described above for the oxidation of 6-nitroveratraldehyde, to give piperonylic acid (32 g.), which was then nitrated by Jobst and Hesse's method (*loc. cit.*) to 6-nitropiperonylic acid, m. p. 172°, in 60% yield. A suspension of 6-nitropiperonylic acid (10 g.) in benzene (30 c.c.) was boiled under reflux with thionyl chloride (10 g.) until evolution of hydrogen chloride had ceased. After filtration and evaporation at 70° under reduced pressure, more benzene (20 c.c.) was added and the evaporation repeated. The residual 6-nitropiperonyloyl chloride, obtained as a yellow oil (11 g.), in benzene (20 c.c.) was added to ethereal diazomethane (200 c.c.),

prepared from nitrosomethylurea (20 g.), at 0—5°. Nitrogen was evolved and yellow needles separated. After 3 hr. these were collected and recrystallisation from benzene gave *ω-diazo-3 : 4-methylenedioxy-6-nitroacetophenone* (9·5 g.), m. p. 133—134° (decomp.) (Found : C, 46·1; H, 2·3. $C_9H_5O_5N_3$ requires C, 46·2; H, 2·1%). The diazo-ketone (10 g.) and 2-(3 : 4-methylenedioxyphenyl)ethylamine (7 g.), as for the preparation of (X), gave the *amide* as a grey solid. Recrystallisation from pyridine gave needles (9 g.), m. p. 203—206° (Found : C, 57·8; H, 4·15. $C_{18}H_{16}O_7N_2$ requires C, 58·2; H, 4·3%).

*3-Benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide* (XXV).—A mixture of 2-nitro*iso*vanillin (5 g.; Pschorr and Stöhrer, *Ber.*, 1902, **35**, 4393), alcohol (20 c.c.), water (25 c.c.), benzyl chloride (25 g.), and sodium carbonate (5 g.) was boiled under reflux for 4 hr. Water (80 c.c.) was added and excess of benzyl chloride was removed with steam. The residual oil solidified and crystallisation from alcohol and then from benzene–light petroleum (b. p. 60—80°) gave *O-benzyl-2-nitroisovanillin* (6 g.) in plates, m. p. 102—103° (Found : C, 62·5; H, 4·4. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·5%). In similar manner 6-nitro*iso*vanillin (5 g.) gave its *benzyl ether* (6 g.), plates m. p. 133—134° (Found : C, 62·6; H, 4·4%). *O*-Benzyl-2-nitro*iso*vanillin (5 g.) was oxidised with silver nitrate in alkaline solution as described above for the oxidation of *O*-benzylvanillin. The acid was purified by crystallisation of the sodium salt from hot water. Acidification gave *O-benzyl-2-nitroisovanillic acid* (4 g.), which crystallised from aqueous alcohol in needles, m. p. 186° (Found : C, 59·6; H, 4·25. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3%). This acid (5 g.) was converted into the acid chloride (4·2 g.), needles, m. p. 122—123°, by the method used above with *O*-benzyl-2-nitrovanillic acid, and thence into *3-benzyloxy-ω-diazo-4-methoxy-2-nitroacetophenone* (3·6 g.) by the method used in the previous examples. The diazo-ketone separated from benzene in pale yellow needles, m. p.123—124° (decomp.) (Found : C, 58·9; H, 4·0. $C_{16}H_{13}O_5N_3$ requires C, 58·7; H, 4·2%). The diazo-ketone (7 g.) and 2-(3 : 4-methylenedioxyphenyl)ethylamine (4 g.), by the procedure used for (X), gave the *amide* (4 g.), plates (from aqueous alcohol), m. p. 106—107° (Found : C, 64·9; H, 4·95. $C_{25}H_{24}O_7N_2$ requires C, 64·7; H, 5·2%).

The Bischler–Napieralski–Pschorr reaction.

*Attempted Ring Closure of 3 : 4-Dimethoxy-2-nitrophenyl-*N*-phenethylacetamide and of o-Nitrophenyl-*N*-phenethylacetamide.*—Attempted ring closure of 3 : 4-dimethoxy-2-nitrophenyl-*N*-phenethylacetamide (1 g.) with phosphoric oxide in boiling sulphur-free xylene, followed by addition of ice and concentrated hydrochloric acid, gave, on evaporation of the xylene layer, a non-basic compound $C_{18}H_{18}O_4N_2$ (0·5 g.), yellow needles, m. p. 123—124° (from alcohol) (Found : C, 66·6; H, 5·6. Calc. for $C_{18}H_{18}O_4N_2$: C, 66·25; H, 5·5%). Basification of the aqueous acid gave only a slight turbidity (cf. Kay and Pictet, *loc. cit.*, and Callow, Gulland, and Haworth, *J.*, 1929, 1444). Similar results were obtained when concentrated sulphuric acid, fused zinc chloride, phosphorus oxychloride, polyphosphoric acid, and a mixture of phosphorus oxychloride and polyphosphoric acid were used as dehydrating agents in xylene or toluene.

Similar experiments carried out on *o*-nitrophenyl-*N*-phenethylacetamide failed to effect ring-closure, and unchanged amide was in most cases recovered.

*Ring Closure of Phenyl-*N*-phenethylacetamide with Polyphosphoric Acid.*—A mixture of polyphosphoric acid (10 g.) and phenyl-*N*-phenethylacetamide (5 g.) in dry xylene (30 c.c.) was boiled under reflux for 1 hr., after which it was poured into water (30 c.c.) and heated to 70° with concentrated hydrochloric acid (5 c.c.). The aqueous layer was separated, filtered, made alkaline with aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried extract left 1-benzyl-3 : 4-dihydro*iso*quinoline (1·8 g.), b. p. 174—176°/8 mm. (picrate, m. p. 174—175°) (cf. Pictet and Kay, *Ber.*, 1909, **42**, 1977).

1-(4-Benzyloxy-3-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxyisoquinoline (XXVI; R = MeO, R′ = Ph·CH_2·O, R″ = H).—A solution of 4-benzyloxy-3-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (5 g.) in dry alcohol-free chloroform (30 c.c.) to which phosphorus pentachloride (10 g.) had been added was kept in a stoppered flask at room temperature for 4 days. Pressure was released every 12 hr. Crushed ice (100 g.) was added to the ice-cooled mixture and, when the vigorous reaction had subsided, the mixture was allowed to attain room temperature. Chloroform and phosphorus oxychloride were removed at 30° under reduced pressure. The gum which separated was dissolved in hot alcohol (30 c.c.) containing concentrated hydrochloric acid (2 c.c.), boiled with charcoal, and filtered. The substituted *isoquinoline hydrochloride* separated on cooling in pale yellow needles (3·5 g.), m. p. 191—192° (Found : C, 61·9; H, 4·8; N, 6·05; Cl, 7·7.

$C_{25}H_{22}O_6N_2$,HCl requires C, 62·1; H, 4·6; N, 5·8; Cl, 7·6%). The free *base* was liberated by the dropwise addition of dilute aqueous ammonia to a hot alcoholic solution of the hydrochloride. Crystallisation from aqueous alcohol gave the base in off-white needles, m. p. 138—140° (Found: N, 6·6. $C_{25}H_{22}O_6N_2$ requires N, 6·3%). The *methiodide*, prepared by boiling a methyl-alcoholic solution of the base with methyl iodide for 2 hr., separated from methyl alcohol–acetone in pale yellow needles, m. p. 160—161° (Found: N, 4·9. $C_{25}H_{22}O_6N_2,CH_3I$ requires N, 4·9%).

1-(2-*Amino*-4-*benzyloxy*-3-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*isoquinoline (XXVII; R = MeO, R′ = Ph·CH_2·O, R″ = H, X = Me).—Concentrated hydrochloric acid was added to a solution of 1-(4′-benzyloxy-3′-methoxy-2′-nitrobenzyl)-6 : 7-methylenedioxy*iso*quinoline methiodide (1 g.) in dioxan (20 c.c.) until a faint turbidity appeared. Zinc dust (5 g.) was added in small portions to the ice-cooled mixture until the yellow colour was completely discharged. Water (30 c.c.) was added and the mixture was filtered. The filtrate was covered with a layer of ether in a separating funnel and made alkaline with ammonia, the temperature being kept below 15°. The ether layer was removed and the aqueous layer was extracted a second time with ether. The combined ethereal extracts were dried (K_2CO_3) and the ether removed. The base, which was obtained as a brown oil and which could be diazotised and coupled with β-naphthol, was dissolved in hot alcohol (20 c.c.) and added to a solution of picrolonic acid (1 g.) in boiling alcohol (10 c.c.). On cooling, 1-(2-*amino*-4-*benzyloxy*-3-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*isoquinolinium *dipicrolonate* (0·7 g.) separated, which crystallised from acetone in yellow needles, m. p. 185—186° (Found: C, 57·7; H, 4·95. $C_{26}H_{28}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 57·5; H, 4·6%). A similar reduction was effected with glacial acetic acid (20 c.c.) in place of dioxan (20 c.c.).

(±)-3-*Hydroxy*-4-*methoxy*-5 : 6-*methylenedioxyaporphine* (iso*Bulbocapnine*) (XXVIII; R = MeO, R′ = HO, R″ = H, X = Me).—A suspension of the above dipicrolonate (1·8 g.) in cold methyl alcohol (20 c.c.) was ground in a mortar with concentrated sulphuric acid (1 c.c.). The precipitated picrolonic acid was filtered off and washed with a small quantity of methyl alcohol, which was added to the filtrate. A solution of barium nitrite (0·34 g.) in water (1 c.c.) was added to the solution, which was kept at 0° for 4 hr., after which catalytic copper powder (0·5 g.) was added. The mixture was boiled under reflux for ½ hr., nitrogen being evolved. After addition of water (20 c.c.) the copper powder and barium sulphate were removed by filtration. The filtrate, in a separating funnel, was covered with a layer of ether and made alkaline with dilute aqueous sodium hydroxide. The ethereal layer was removed and the aqueous layer again extracted several times. The combined ethereal extracts were washed with water and dried (Na_2SO_4). Removal of the ether left a pale brown oil. Concentrated hydrochloric acid (10 c.c.) was added and the solution was warmed to 70° for ½ hr., during which the solution became turbid and benzyl chloride was liberated. Water (15 c.c.) was added to the cold solution, which was then made alkaline with aqueous ammonia and extracted three times with ether (25 c.c.). Removal of the ether from the combined dried (Na_2SO_4) extracts left an almost colourless gum which when scratched under light petroleum (b. p. 40—60°) became crystalline. Recrystallisation from ethylene dichloride–light petroleum (b. p. 40—60°) and then twice from alcohol–ether gave (±)-3-*hydroxy*-4-*methoxy*-5 : 6-*methylenedioxyaporphine* (40 mg.) in colourless tablets, m. p. 165—166°, soluble in acetic acid and aqueous sodium hydroxide (Found: C, 69·7; H, 5·6. $C_{19}H_{19}O_4N$ requires C, 70·15; H, 5·8%).

1-(4-*Benzyloxy*-3-*methoxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline (XXVI; R = H, R′ = Ph·CH_2·O, R″ = MeO).—By use of the methods previously described 4-benzyloxy-3-methoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (5 g). and phosphorus pentachloride (10 g.) in dry chloroform (30 c.c.) gave the substituted *dihydro*isoquinoline *hydrochloride* (2·6 g.) in plates, m. p. 224—226° (from alcohol) (Found: Cl, 7·8. $C_{25}H_{22}O_6N_2$,HCl requires Cl, 7·6%). The free *base*, liberated from an alcoholic solution of the hydrochloride with ammonia, crystallised from ethylene dichloride–methyl alcohol in plates, m. p. 164—165° (Found: C, 67·3; H, 4·8. $C_{25}H_{22}O_6N_2$ requires C, 67·1; H, 4·9%). The *methiodide*, prepared as above, separated from acetic acid in yellow needles, m. p. 180—181° (Found: C, 54·5; H, 4·6. $C_{25}H_{22}O_6N_2,CH_3I$ requires C, 54·4; H, 4·4%).

1-(6-*Amino*-4-*benzyloxy*-3-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*isoquinoline (XXVII; R = H, R′ = $PhCH_2$·O, R″ = MeO, X = Me).—The foregoing methiodide (1 g.) was reduced in glacial acetic acid (25 c.c.) with zinc dust (6 g.) as described in the previous example and the *tetrahydro*isoquinolinium *dipicrolonate* (0·8 g.) was obtained in needles, m. p. 176°, from a large volume of alcohol (Found: C, 56·9; H, 4·4. $C_{26}H_{28}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 57·5; H, 4·6%).

(±)-3-*Hydroxy*-2-*methoxy*-5 : 6-*methylenedioxyaporphine* (XXVIII; R = H, R′ = HO, R″ = MeO, X = Me).—By the method described in the previous example the preceding dipicrolonate (2 g.) gave (±)-3-hydroxy-2-methoxy-5 : 6-methylenedioxyaporphine (0·15 g.), which separated from ethylene dichloride–light petroleum (b. p. 40—60°) in needles, m. p. 126—129° after softening at 117°. The base became brown in air and was readily soluble in both acetic acid and aqueous sodium hydroxide. Because of its instability it was analysed as the *picrolonate* which separated from alcohol in yellow needles, m. p. 198—199° (decomp.) (Found: C, 58·8; H, 4·4. $C_{19}H_{19}O_4N,C_{10}H_8O_5N_4$ requires C, 59·1; H, 4·6%).

1-(3 : 4-*Dimethoxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline (XXVI; R = H, R′ = MeO, R″ = MeO).—By the methods described above, 3 : 4-dimethoxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (9 g.) and phosphorus pentachloride (15 g.) in dry chloroform (30 c.c.) gave 1-(3 : 4-*dimethoxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline *hydrochloride* (5 g.), which separated from dilute hydrochloric acid in yellow plates, m. p. 213—214° (Found: Cl, 9·1. $C_{19}H_{18}O_6N_2$,HCl requires Cl, 8·7%). The free *base*, liberated with ammonia, was obtained in white leaflets, m. p. 198—202° (darkening at 195°), from alcohol containing a small quantity of ethylene dichloride (Found: C, 61·4; H, 5·0. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9%). The *methiodide*, prepared as described in the previous examples, separated from acetic acid in yellow needles, m. p. 208—209° (Found: I, 25·0. $C_{19}H_{18}O_6N_2,CH_3I$ requires I, 25·2%). Reduction of the methiodide (1 g.) with zinc dust (6 g.) in dilute hydrochloric acid (1 : 1; 30 c.c.) as described above, gave 1-(6-amino-3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline dihydrochloride (0·2 g.), m. p. 249—250° (decomp.). Haworth, Perkin, and Rankin (*J.*, 1925, **127**, 2022) record m. p. 250° (decomp.) for this compound prepared by another method.

1-(6-*Amino*-3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*isoquinoline (XXVII; R = H, R′ = MeO, R″ = MeO, X = H).—Zinc dust (4 g.) was added in small portions to a hot solution of 1-(3 : 4-dimethoxy-6-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline (1 g.) in a mixture of water (15 c.c.) and concentrated hydrochloric acid (15 c.c.). When the yellow colour was discharged the mixture was cooled, filtered, transferred to a separating funnel, and covered with ether. Concentrated aqueous ammonia was then added until the precipitated zinc hydroxide had dissolved. The white solid which remained undissolved was collected, but darkened on exposure to air. It was dissolved in alcohol, filtered, and added to a boiling alcoholic solution (10 c.c.) of picrolonic acid (1 g.). On cooling, the *tetrahydro*isoquinolinium *dipicrolonate* separated; it (0·5 g.) had m. p. 170—190°, depending on rate of heating (Found: C, 53·6; H, 4·5. $C_{19}H_{22}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 53·8; H, 4·5%).

(±)-2 : 3-*Dimethoxy*-5 : 6-*methylenedioxynoraporphine* (*Actinodaphnine Methyl Ether*) (XXVIII; R = H, R′ = MeO, R″ = MeO, X = H).—A solution of 1-(3 : 4-dimethoxy-6-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline (2 g.) in dilute hydrochloric acid (1 : 1; 30 c.c.) was reduced with zinc dust (5 g.) as described above. After filtration the solution was cooled to 0° and diazotised with a solution of barium nitrite (0·52 g.) in water (2 c.c.). The diazonium solution was set aside for 15 min. and then kept at 60° until evolution of nitrogen was complete (1 hr.). The dark solution was heated to the b. p. and zinc dust (1 g.) was added. The solution, which became yellow, was made alkaline with ammonia and extracted several times with ether. The combined extracts were washed successively with aqueous sodium hydroxide and with water. Removal of the ether from the dried (K_2CO_3) extract left a green gum. This was dissolved in a warm mixture of ethylene dichloride and light petroleum (b. p. 60—80°), and the green oil which separated on cooling was removed by decantation. This operation was repeated with the addition of more light petroleum until a clear and almost colourless solution was obtained. Evaporation of the solvent then left a colourless gum which solidified. Recrystallisation from ether–alcohol (3 : 1) gave (±)-2 : 3-*dimethoxy*-5 : 6-*methylenedioxynoraporphine* (0·1 g.) in white needles, m. p. 114—115° (Found: C, 70·6; H, 5·7. $C_{19}H_{19}O_4N$ requires C, 70·15; H, 5·8%).

1-(3 : 4-*Methylenedioxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline (XXVI; R = H, R′R″ = ·O·CH_2·O·).—A suspension of 3 : 4-methylenedioxy-6-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide (8 g.) in dry chloroform (30 c.c.) with phosphorus pentachloride (15 g.) was kept for 4 days at 0°. Crushed ice (50 g.) was added and the chloroform and phosphorus oxychloride were removed under reduced pressure at 50°. The dark aqueous solution was made nearly neutral with ammonia, boiled with charcoal, and filtered. Addition of further ammonia to the filtrate precipitated a mauve-coloured oil, which solidified to an amorphous powder. This was dissolved in acetic acid (10 c.c.) and alcohol (10 c.c.),

boiled with charcoal, and filtered. Basification of the filtrate with dilute aqueous ammonia precipitated the *dihydroisoquinoline* (1·9 g.), which crystallised from methyl alcohol containing a small quantity of ethylene dichloride in plates, m. p. 159° (decomp.) (Found : C, 60·7; H, 3·8. $C_{18}H_{14}O_6N_2$ requires C, 61·0; H, 4·0%). The same product was obtained in poorer yield by Barger and Weitnauer's method (*Helv. Chim. Acta*, 1939, **22**, 1039). The *methiodide*, prepared as in the preceding examples, crystallised from methyl alcohol containing a small quantity of acetone in yellow needles, m. p. 228—229° (Found : I, 25·9. $C_{18}H_{14}O_6N_2,CH_3I$ requires I, 25·6%).

1-(6-*Amino*-3 : 4-*methylenedioxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*-*isoquinoline* (XXVII; R = H, R′R″ = ·O·CH_2·O·, X = Me).—To a suspension of the above methiodide (2 g.) in a mixture of concentrated hydrochloric acid (15 c.c.) and water (15 c.c.) at 40°, was added zinc dust (5 g.) in small portions. The temperature rose to 80° and the solution was then boiled and more zinc dust (1 g.) added. After filtration the base was liberated with ammonia under ether as in the previous examples, and converted into the dipicrolonate. Crystallisation from a large quantity of alcohol gave the *tetrahydroisoquinolinium dipicrolonate* (2 g.) in yellowish plates, m. p. 169° (decomp.) (Found : C, 53·5; H, 4·4. $C_{19}H_{20}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 53·6; H, 4·15%).

(±)-2 : 3-5 : 6-*Bismethylenedioxyaporphine* (XXVIII; R = H, R′R″ = ·O·CH_2·O·, X = Me).—The above dipicrolonate (2 g.), by the methods described in the previous examples gave, on evaporation of the dried (Na_2SO_4) ethereal extract, a pale yellow gum which solidified. Crystallisation several times from alcohol–ether (1 : 1) gave (±)-2 : 3-5 : 6-*bismethylenedioxy*-*aporphine* (50 mg.) in needles, m. p. 181—182° (Found : C, 70·5; H, 5·5. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3%).

Preliminary attempts to convert 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-2-(3 : 4-methylenedioxyphenyl)ethylacetamide into 1-(3-benzyloxy-4-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline by the use of phosphorus pentachloride in chloroform, as in the previous examples, resulted in debenzylation.

KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON, W.C.2.

[*Received, December* 16*th*, 1953.]

The Near-ultra-violet Absorption Spectra of Some Heterocyclic Compounds. Part I. Benzoxazoles.

BY R. PASSERINI.

[Reprint Order No. 5013.]

The ultra-violet absorption spectra of benzoxazole and many mono- and di-substituted derivatives have been investigated to 210 mμ, the substituents being CH_3, C_6H_5, NO_2, SR, and NR_2 (R = H, alkyl, aryl, or acyl). Interpretations are offered on the basis of essentially localised chromophores, with resonance interaction between them in suitable structural circumstances.

FOLLOWING previous work on the electronic spectra of some benziminazoles (Mangini Montanari, and Passerini, *Atti Accad. Lincei*, 1952, **12**, 411), a systematic survey of the spectra of heterocyclic compounds is being undertaken, and this paper relates to benzoxazoles. Earlier records of these spectra (Behaghel and Schneider, *Ber.*, 1936, **69**, 93; Ramart-Lucas and Vantu, *Bull. Soc. chim.*, 1936, **3**, 1165) are too fragmentary, and such few spectra as are recorded are inadequate for the discussions which follows. The new data are recorded in Tables 1 and 2, and in the figure.

Benzoxazole and 2-*Methylbenzoxazole* (Table 1, Nos. 1 and 2).—These spectra are closely similar. The first absorption system, around 270 mμ, is obviously derived from the B_{2u} benzene system, and shows the characteristic vibrational structure. Thus the benzo-ring, and not the hetero-ring, is regarded as the basic chromophore. The moderate bathochromic shift and intensification, relative to the benzene system at 255 mμ, would be a normal result of weak conjugation by the hetero-atoms with the benzo-ring. Similar effects are found in anisole (Robertson, Sheriff, and Matsen, *J. Amer. Chem. Soc.*, 1950, **72**, 1539; Cerniani, Passerini, and Righi, *Gazzetta*, 1954, **84**, in the press), benzofuran

(Andrisano and Pappalardo, *ibid.*, 1953, **83**, 108), and benziminazole (Steck, Nachod, Ewing, and Gorman, *J. Amer. Chem. Soc.*, 1948, **70**, 3406; Mangini *et al.*, *loc. cit.*).

The second absorption system at 231 mμ has about the position and intensity to be expected if it is derived from the second absorption system of benzene, which, according to our present knowledge, may belong to either species B_{1u} or E_{2g}, and has its onset at 203 mμ. This tentative argument is somewhat strengthened by the consideration that it seems possible to interpret the spectra of all the derivatives described below without

TABLE 1.

(Solutions are in ethyl alcohol except where otherwise indicated.)

2-*X*-Benzoxazoles.

X =	M. p.	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{min.}$	log $\varepsilon_{min.}$
1[a] H	182·5° *	231	3·90	218	3·74
		263	3·38	253	3·12
		270	3·53	266	3·32
		276	3·51	274	3·08
2[b] CH_3	201 *	231	3·97	218	3·73
		264	3·43	253	3·12
		270	3·61	266	3·42
		276	3·64	275	3·40
3[c] C_6H_5	102	234	3·86	227	3·85
		(260)	4·05	243	3·78
		292	4·34	295	4·33
		299	4·35		
		(310)	4·08		
4[d] C_6H_4Me (*o*)	69	236	3·88	233	3·87
		(270)	4·13	243	3·86
		292	4·30		
		(313)	4·10		
5[d] C_6H_4Me (*m*)	71	240	3·83	234	3·84
		(270)	4·13	244	3·78
		294	4·36	296	4·35
		(310)	4·00		
6[e] C_6H_4Me (*p*)	114	240	3·83	230	3·76
		(275)	4·13	244	3·79
		295	4·36	298	4·35
		302	4·37		
		(313)	4·10		
7[f] C_6H_4·OH (*o*)	124	263	4·05	245	3·72
		272	4·11	266	4·05
		281	4·17	277	4·08
		285	4·17	283	4·15
		293	4·30	288	4·10
		319	4·23	299	3·96
		331	4·18	326	4·18
7 C_6H_4·OH (*o*) aq. N-HCl	—	(263)	4·06	276	4·10
		274	4·13	288	4·12
		286	4·18	298	3·99
		292	4·30		
		318	4·26		
		(339)	4·19		
C_6H_4·O⁻ (*o*) aq. N-NaOH	—	220	4·40	260	3·92
		286	4·06	306	3·00
		352	4·08		
8[d] C_6H_4·OH (*p*)	250°	(273)	4·07	240	3·43
		305	4·47		
9[e] C_6H_4·OMe (*p*)	99	(275)	4·13	238	3·54
		306	4·51		
10[e] C_6H_4·NO_2 (*m*)	211	222	4·20	218	4·20
		265	4·27	244	4·06
		295	4·32	275	4·24
11[e] C_6H_4·NO_2 (*p*)	268	232	4·13	218	4·01
		327	4·33	268	3·53
12[e] C_6H_4·NH_2 (*m*)	178	228	4·31	244	4·15
		256	4·19	270	4·12
		296	4·36		
		(310)	3·77		
13[e] C_6H_4·NH_2 (*p*)	170	222	4·07	254	3·26
		(276)	3·74		
		327	4·50		
14[e] C_6H_4·NHAc (*p*)	212	(225)	4·15	247	3·50
		316	4·51		
15[f] C_6H_4·NMe_2 (*p*)	183	230	4·02	270	3·24
		(308)	3·97		
		345	4·66		

5-Nitro-2-*X*-benzoxazoles.

16[d] H	127	224	4·39	250	3·59
		270	3·84		
		(335)	2·60		
17[e] CH_3	154	226	4·42	252	3·56
		274	3·84		
		(335)	2·83		
18[e] C_6H_5	172	214	4·16	232	3·86
		269	4·48		
19[f] C_6H_4·NO_2 (*p*)	258	232	4·18	216	4·12
		(300)	4·20	255	4·03
		324	4·27		
20[f] C_6H_4·NHAc (*p*)	259	225	4·22	248	3·85
		310	4·50		

6-Nitro-2-*X*-benzoxazoles.

21[h] H	125	282	4·01	242	3·20
22[g] CH_3	151	290	4·04	246	3·39
23[e] C_6H_5	180	258	4·09	238	3·95
24[f] C_6H_4·NO_2 (*p*)	221	332	4·50	252	3·86

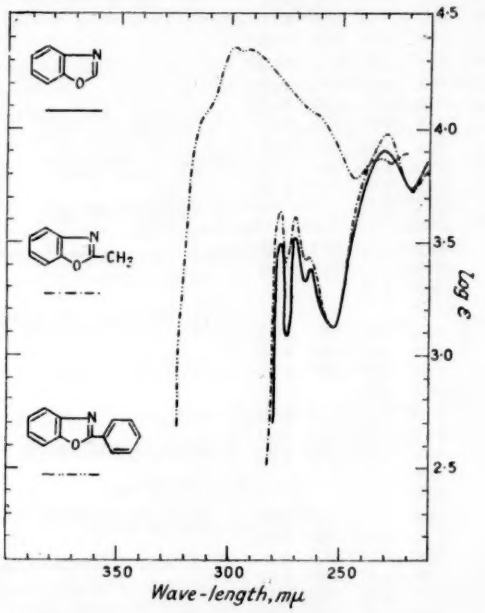
5-Methyl-2-*p*-nitrophenylbenzoxazole.

25[f]		234	4·12	222	4·06
		334	4·33	273	3·64

[a] Bamberger, *Ber.*, 1903, **36**, 2051. [b] Light & Co., redistilled. [c] Stephens and Bower, *J.*, 1949, 2971. [d] See p. 2260. [e] Holljes and Wagner, *J. Org. Chem.*, 1944, **9**, 31. [f] Specimen kindly supplied by Dr. F. F. Stephens of Glaxo Laboratories. [g] Phillips, *J.*, 1930, 2685. [h] *Chem. Zentr.*, 1927, II, 1308; cf. F.P. 575,663. * B. p.s.

assuming that a specific excitation of the aromatic π shell of the hetero-ring is under observation.

5- *and* 6-*Nitro-benzoxazole and* -2-*methylbenzoxazole* (Table 1, Nos. 16, 17, 21, and 22).—These four spectra are similar. The first absorption appears as a moderately strong, structureless band near 270 mμ. This is a normal result of that strong conjugation between a nitro-group and a benzene ring, which is best regarded as producing a combined nitrophenyl chromophore (Mangini and Passerini, *J.*, 1952, 1168). The insensitiveness of this absorption to the position of the nitro-group shows that through-conjugation with the hetero-atoms is weak: if it were strong, as, *e.g.*, in *p*-nitrophenol, we should expect a large further bathochromic shift (cf. Burawoy and Chamberlain, *J.*, 1952, 2310). The fact that the spectra are scarcely changed in concentrated sulphuric acid points in the same direction. Theoretically, such through-conjugation should be weak, since the only non-polar, non-bridged (and therefore the main) valency structure of the hetero-ring (I) stereo-



electronically restricts nitrogen, as well as oxygen, conjugation to that fundamentally involved in the π-shell of the hetero-ring.

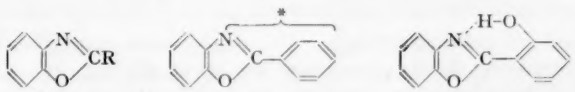
2-*Phenyl-*, 2-o-, -m-, *and* -p-*Methyl-*, 2-o- *and* -p-*Hydroxy-phenyl-*, *and* 2-p-*Methoxy-phenyl-benzoxazole* (Table 1, Nos. 3—9).—The spectra of all these 2-aryl derivatives are generally similar, with one notable exception mentioned below, and they differ remarkably from the spectra of the non-arylated benzoxazoles. This exception apart, they are characterised by a strong and very broad first absorption near 300 mμ. It is believed that this contains, as a weaker component, possibly to be seen in the shoulders on the short-wave sides of the main bands, the already discussed first band-system of the benzo-ring chromophore. The stronger and longer-wave absorption is ascribed to the newly introduced benzylidene-imine chromophore [with asterisk in (II)]. There are no stereo-electronic restrictions on conjugation between the phenyl ring and the hetero-ring, and, for the reason mentioned in the preceding paragraph, we thus expect conjugation to extend mainly to the nitrogen atom. The interaction is strong enough to justify our regarding it as producing a new combination chromophore. However, the C:N-unit is only weakly electronegative, and thus through-conjugation with *para*-situated hydroxyl or methoxyl groups modifies the spectrum only slightly.

It is the *ortho*-hydroxyl substituent which produces the striking spectral modification, breaking the broad band up into two band systems, of which the short-wave one shows well-developed vibrational structure, while the long-wave one is moved slightly to longer waves and is weakened. It may be suggested that these effects arise from hydrogen bonding (III), which, by charging the nitrogen atom positively, reduces the benzylidene-imine conjugation, and allows the benzo-ring absorption to appear separately, perhaps with a superimposed first absorption (B_{2u} type) of the phenyl ring chromophore, acting to some extent independently.

m- *and* p-*Amino-*, p-*Acetamido-*, *and* p-*Dimethylamino-benzoxazole* (Table 1, Nos. 12—15).—The three forms of *p*-amino-substituent produce bathochromic shifts of the long-wave band ascribed above to the benzylidene-imine chromophore. With methoxy- and hydroxy-substituents included for comparison, the displacements are in the order $NMe_2 > NH_2 > NHAc > OMe,OH > H$, the maxima appearing respectively at **345**, **327**, **316**, **306**, **305**, and **299** mμ. The order of the groups is that of *o* : *p*-orienting power in electrophilic substitution, as far as this is known (Ingold and Ingold, *J.*, 1926, 1310). Evidently the *p*-amino-group, except when acylated, can enter strongly into the benzylidene-imine conjugation.

The *m*-amino-group cannot, of course, do so; and accordingly, the spectrum of this substitution-product is very different. It consists of a dominant long-wave band, which, from its position and intensity, may be correlated with the main band, ascribed to the benzylidene-imine chromophore in the unsubstituted 2-phenyl compound, and two overlapped shorter-wave systems, which might arise from the aniline and the benzo-ring chromophores.

5-, 6-, 3'-, *and* 4'-*Nitro-derivatives of* 2-*Phenylbenzoxazole* (Table 1, Nos. **10**, **11**, **18**—**20**, and **23**—**25**).—A *m*- or *p*-nitro-substituent in the phenyl ring produces spectral effects sufficiently similar to those of correspondingly situated amino-groups to render detailed discussion unnecessary. Just as the nitro-group like the amino-group is conjugated heavily with the simple benzene ring, so both groups must be considered to form united and more complex chromophores with the benzylidene-imine system.



(I) (II) (III)

The 5- and 6-nitro-derivatives of 2-phenyl- or of substituted 2-phenyl-benzoxazoles show spectra which, in first approximation, can be understood as superposed effects of excitation of the already discussed chromophores, separately present in 5- or 6-nitro-benzoxazole and in 2-phenylbenzoxazole. In second approximation, however, the nitro-benzo- and benzylidene-imino-chromophores interact, with the result that the two bands are found, not at 300 and 280 mμ, but further apart, with certain transfers of intensity between them. The separation is relatively small in the 5-nitro-compounds, but considerable in the 6-nitro-derivatives, the two bands in 6-nitro-2-phenylbenzoxazole itself appearing at 322 and 258 mμ. This larger separation is to be expected, since the 6-nitro-group of the one elementary chromophore is formally conjugated with the imino-nitrogen atom of the other, and hence resonance between the unit chromophores, thus overlapped, is readily possible.

2-*Methylthio-* *and* 2-*Phenylthio-benzoxazole* (Table 2, Nos. 1 and 2).—The spectra of these two benzoxazoles are similar. They show that the 2-thio-group modifies the benzoxazole spectrum similarly to the 2-phenyl group. The main difference is that the long-wave band-system, near 280 mμ, now attributed to the introduced thioamide type of conjugation is narrower than that of the benzylidene-imine chromophore, and does not wholly overlap the benzo-ring system, which can be seen near 250 mμ.

2 *Anilinobenzoxazole* (Table 2, No. 4).—This spectrum is similar to those of the 2-thio-compounds, except that the long-wave system, which must here be attributed to the newly introduced amidine type of conjugation, appears at slightly longer wave-length,

TABLE 2.

2-*X*-Substituted benzoxazoles.

X =	M. p.*	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{min.}$	log $\varepsilon_{min.}$	X =	M. p.*	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{min.}$	log $\varepsilon_{min.}$
1 [a] SMe	—	249	4·07	236	3·75	5 [d] NH·C_6H_4Me (*m*)	145°	264	4·30	235	3·57
		278	4·09	264	3·81			290	4·42	272	4·12
		286	4·06	282	3·96			296	4·41		
2 [b] SPh	—	247	4·09	228	3·96	6 [d] NH·C_6H_4Me (*p*)	182	263	4·32	235	3·56
		280	4·10	265	3·96			288	4·44	272	4·13
		286	4·11	283	4·09	7 [e] NH·C_6H_4·NO_2 (*m*)	192—	259	4·38	230	3·93
3 [b] S·C_6H_4Me (*p*)	—	247	4·18	232	4·01		194	287	4·50	272	4·26
		279	4·16	268	4·02			354	3·13	320	2·95
		286	4·17	283	4·13	8 [b] NH·C_6H_4·NO_2 (*p*)	230—	245	4·21	224	3·91
4 [c] NHPh	175°	261	4·31	235	3·54		231	276	3·78	272	3·76
		288	4·41	272	4·11			284	3·72	282	3·71
		296	4·40					356	4·31	294	3·44

6-Nitro-2-*X*-benzoxazoles.

9 [f] SMe	123—	243	4·03	227	3·97	15 [b] NH·C_6H_4Me (*o*)	172—	254	4·14	226	3·96
	125°	321	4·18	265	3·43		173	354	4·24	284	3·36
10 [b] SPh	121—	241	4·13	228	4·07	16 [b] NH·C_6H_4Me (*m*)	214—	262	4·29	226	3·85
	122	320	4·22	274	3·78		215	364	4·28	296	3·39
11 [b] S·C_6H_4Me (*o*)	106—	242	4·12	232	4·07	17 [b] NH·C_6H_4Me (*p*)	215—	263	4·27	226	3·86
	108	318	4·17	282	3·84		216	366	4·24	298	3·44
12 [b] S·C_6H_4Me (*m*)	110—	241	4·10	230	4·06	18 [e] NH·C_6H_4·NO_2 (*m*)	234	260	4·37	226	4·09
	112	320	4·19	273	3·76			349	4·30	298	3·79
13 [b] S·C_6H_4Me (*p*)	142—	240	4·12	234	4·11	19 [b] NH·C_6H_4·NO_2 (*p*)	299—	228	4·19	218	4·14
	143	322	4·23	271	3·61		300	366	4·49	272	3·58
14 [b] NHPh	224—	261	4·30	225	3·84			466	3·64	428	3·45
	225	359	4·29	292	3·38						

[a] Beilenson and Hamer, *J.*, 1939, 143. [b] Cerniani and Passerini, *Annali*, 1954, **44**, 3. [c] Kalchoff, *Ber.*, 1883, **16**, 1825. [d] Deck and Dains, *J. Amer. Chem. Soc.*, 1933, **55**, 4986. [e] See p. 2261. [f] Bower and Stephens, *J.*, 1951, 325.

* B. p.s. of compounds as numbered were: (1) 139—140°/20 mm.; (2) 193—196/14 mm.; (3) 215—216/14 mm.

about 292 mμ, and is somewhat stronger. The shorter-wave system, which may be again ascribed to the benzo-ring chromophore, now appears at 260 mμ.

Methyl- and Nitro-substitution Products of 2-Phenylthio- and 2-Anilino-benzoxazole (Table 2, Nos. 3 and 5—19).—The spectra of these derivatives present no unexpected features, and could be discussed on lines similar to those above.

EXPERIMENTAL

Compounds already recorded in the literature have been prepared as indicated in the footnotes to Tables 1 and 2. New substances were prepared as follows. 2-o-*Tolylbenzoxazole* was prepared by Hölljes and Wagner's general method (*J. Org. Chem.*, 1944, **9**, 31) for benzoxazole syntheses. *o*-Aminophenol (5 g.) and *o*-tolunitrile (5 g.) were heated in a sealed tube at 190—200° for 5 hr. The product was distilled under reduced pressure, b. p. 163—166°/15 mm.; it crystallised from aqueous ethanol (charcoal) in pale yellow needles, m. p. 69° (Found: N, 6·7. $C_{14}H_{11}ON$ requires N, 6·7%). 2-m-*Tolylbenzoxazole*, similarly prepared, had b. p. 190°/15 mm., and on crystallisation from aqueous ethanol formed pale yellow plates, m. p. 71° (Found: N, 6·7%). 2-p-*Hydroxyphenylbenzoxazole* was prepared by heating *o*-aminophenol with *p*-cyanophenol at 190—200° for 5 hr. The product was extracted with ethanol (100 ml.) by distillation of which it was obtained as a solid, which crystallised from aqueous ethanol in pale pink needles, m. p. 250° (Found: N, 6·7. $C_{13}H_9O_2N$ requires N, 6·6%). A suspension in sodium hydroxide solution (2N) of 2-*p*-hydroxyphenylbenzoxazole was treated with methyl sulphate, the mixture being kept alkaline to phenolphthalein. After 30 min., 2-*p*-methoxyphenylbenzoxazole was removed and crystallised from ethanol; it had m. p. 99° (cf. Stephens and Bower, *J.*, 1950, 1722). 5-*Nitrobenzoxazole* was obtained by distillation at 15 mm. of 2-formamido-4-nitrophenol (5 g.). Crystallisation from ethanol yielded prisms, m. p. 127° (Found: N, 17·1. $C_7H_4O_3N_2$ requires N, 17·1%). For the preparation of 2-m-*nitroanilinobenzoxazole*, 2-chlorobenzoxazole (3 g.) and *m*-nitroaniline (2·7 g.) were heated at 150—160° for 1 hr. The residue, after extraction

with acetic acid, was crystallised from ethanol (charcoal); it had m. p. 193—194° (Found: N, 16·7. $C_{13}H_9O_3N_3$ requires N, 16·5%). For the preparation of 6-*nitro*-2-m-*nitrophenylbenzoxazole* a solution of 2-chloro-6-nitrobenzoxazole (Cerniani and Passerini, *Annali*, 1954, **44**, 3) in ethanol (50 ml.) was boiled with a solution of *m*-nitroaniline (3·5 g.) in ethanol (30 ml.) under reflux for 2 hr. The solid product, removed by filtration, was crystallised from acetic acid, and had m. p. 232—234° (Found: N, 18·7. $C_{13}H_8O_5N_4$ requires N, 18·7%).

Light-absorption Measurements.—A Beckman model D.U. Spectrophotometer was used, hydrogen and tungsten lamps being employed as light sources. Spectra were taken in solutions of concentration 1 in 10^5, in 95% ethanol, or, as noted in the Tables, in N/1-aqueous hydrochloric acid or N/10-aqueous sodium hydroxide. Readings were taken 2 mμ apart. The wavelengths were measured to 0·25 mμ in the important regions of the spectra.

This work has benefited by an exchange of views with Professor C. K. Ingold, F.R.S. The author thanks Dr. F. F. Stephens of Glaxo Laboratories Ltd. for his kind co-operation.

ISTITUTO DI CHIMICA INDUSTRIALE DELL' UNIVERSITA,
BOLOGNA.

[*Received, January 6th*, 1954.]

The Near-ultra-violet Absorption Spectra of Some Heterocyclic Compounds. Part II. Benzothiazoles.*

By A. CERNIANI and R. PASSERINI.

[Reprint Order No. 5014.]

The work of Part I * on benzoxazoles is supplemented by a similar study of benzothiazole and its derivatives. The suggestions made for benzoxazoles concerning the locations of chromophores, their resonance when overlapped, and effect of hydrogen bonding are confirmed for the benzothiazole series. A general bathochromic shift without intensification, from benzoxazole to benzothiazole compounds, which is found in the bands assigned to the benzo-ring chromophore, is attributed to a shift of relative conjugating power of O and S from the order O>S in the ground state of the carbon $2p\pi$ shell, towards the order O<S, as the $2p\pi$ shell becomes enlarged in electronically excited states.

FOR comparison with the spectra (Part I *) of benzoxazole and its substitution products, the near-ultra-violet absorption spectra of benzothiazole and a series of analogous derivatives are now described. These spectra are generally so similar to those obtained in the preceding investigation that a sufficient account of the present work can be given by pointing out the correspondances in general terms and discussing in detail only the more important differences.

Benzothiazole and 2-Methylbenzothiazole (Table 1, Nos. 1 and 2; Fig.).—The spectrum of benzothiazole has been described by Lutskiĭ and Sidorov (cf. *Chem. Abs.*, 1948, **42**, 2516), whose absorption curve differs markedly from that now recorded. The spectrum of 2-methylbenzothiazole has been described by Behaghel and Schneider (*Ber.*, 1936, **69**, 88) and by Lutskiĭ and Sidorov (*loc. cit.*), and, more exactly by Kiprianov and Rozum (cf. *Chem. Abs.*, 1952, **46**, 3400), whose results agree well with those now given. The present results for the two compounds are mutually confirmatory, since the two spectra are almost identical, as would be expected.

The main difference between the spectra of benzoxazole and benzothiazole—a difference which runs all through the spectra of their derivatives, with certain exceptions pointed out below—is that, relatively to the oxygen compound, the sulphur compound shows bathochromic shifts of the bands, without intensification. The first band-system of benzothiazole, which, like that of benzoxazole, is assigned as a transition to the B_{2u}-derived state of the benzo-ring chromophore, has its main maximum at 285 mμ (instead of 270 mμ), the vibrational structure being similar in spacing and intensity distribution to that of the band-system of benzoxazole. The second electronic absorption, the upper state of which we associate, as before, with the benzene state classed as either B_{1u} or E_{2g}, appears at

* Part I, preceding paper.

TABLE 1.

(All spectra measured in ethyl-alcoholic solution.)

2-*X*-Substituted benzothiazoles.

X =	M. p.*	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{min.}$	log $\varepsilon_{min.}$
1[a] H	—	216	4·38	242	3·80
		252	3·76	272	3·17
		285	3·22	291	3·19
		294	3·13		
2[a] CH_3	—	218	4·34	244	3·76
		252	3·87	277	3·10
		283	3·20	289	3·00
		293	3·14		
3[a] C_6H_5	112—113°	226	4·31	222	4·30
		248	3·89	244	3·85
		256	3·90	252	3·88
		297	4·29	261	3·83
4[b] C_6H_4·OH-*o*	131—132	249	3·79	246	3·74
		258	3·85	253	3·77
		288	4·12	262	3·72
		333	4·20	308	3·95
5[b] C_6H_4·OH-*p*	221—222	251	3·71	248	3·70
		258	3·70	256	3·69
		320	4·37	264	3·66
6[b] C_6H_4·NO_2-*m*	184	224	4·42	240	4·05
		254	4·16	260	4·11
		296—300	4·23		
7[b] C_6H_4·NO_2-*p*	228	222	4·36	276	3·59
		(246)	3·93		
		333	4·30		
8[b] C_6H_4·NH_2-*m*	140	230	4·44	266	4·05
		296	4·22		
9[b] C_6H_4·NH_2-*p*	150	222	4·30	274	3·41
		(252)	3·69		
		356	4·56		
10[c] C_6H_4·NMe_2-*p*	173	223	4·32	280	3·31
		(258)	3·80		
		356	4·56		

X =	M. p.*	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{min.}$	log $\varepsilon_{min.}$
11[d] SMe	52°	224	4·31	253	3·78
		(244)	3·94	297	3·91
		278	4·12		
		(287)	4·06		
		299	3·94		
12[e] SPh	—	223	4·41	254	3·86
		281	4·08		
		300	3·96		
13[f] S·C_6H_4Me-*o*	—	221	4·54	252	3·99
		276	4·20	298	4·04
		300	4·05		
14[f] S·C_6H_4Me-*m*	—	221	4·43	254	3·91
		277	4·06	299	3·92
		300	3·93		
15[g] S·C_6H_4Me-*p*	72	224	4·46	254	3·89
		282	4·12	298	3·98
		300	3·99		
16[h] NHPh	160	222	4·29	254	3·61
		(238)	4·24		
		302	4·39		
17[f] NH·C_6H_4Me-*o*	127·5	224	4·29	252	3·78
		(235)	4·20		
		284	4·18		
18[f] NH·C_6H_4Me-*m*	124	220	4·39	254	3·59
		(235)	4·24		
		304	4·40		
19[f] NH·C_6H_4Me-*p*	182—183	222	4·33	254	3·66
		(245)	4·14		
		303	4·40		
20[f] NH·C_6H_4·NO_2-*m*	189—190	235	4·35	254	4·01
		306	4·46	335	3·09
		360	3·16		
21[i] NH·C_6H_4·NO_2-*p*	223	231	4·46	244	4·02
		266	4·13	302	3·44
		372	4·42		

6-Nitro-2-*X*-benzothiazoles.

22[a] H	176°	219	4·21	254	3·43
		285	3·97		
23[a] CH_3	175	218	4·32	255	3·38
		292	4·07		
24[a] C_6H_5	188	225	4·40	252	3·94
		261	3·96	277	3·92
		326	4·38		
25[f] SMe	126	222	4·34	274	3·44
		(244)	4·07		
		330	4·22		
26[f] SPh	104	223	4·46	278	3·59
		(245)	4·12		
		328	4·24		
27[f] S·C_6H_4Me-*o*	101	224	4·53	276	3·68
		(245)	4·17		
		328	4·29		
28[f] S·C_6H_4Me-*m*	132—134	224	4·54	276	3·73
		(245)	4·18		
		328	4·30		
29 S·C_6H_4Me-*p*	144—146	225	4·57	280	3·69
		(245)	4·20		
		328	4·28		

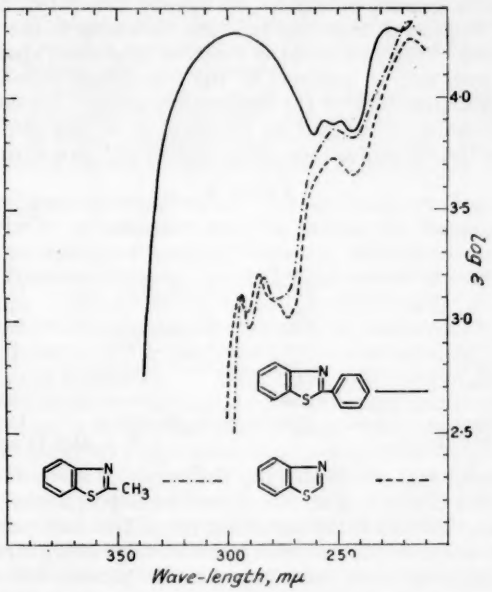
30[a] NHPh	247°	219	4·35	228	4·33
		232	4·33	246	3·94
		273	4·33	301	3·53
		373	4·30		
31[k] NH·C_6H_4Me-*o*	215—216	222	4·39	244	3·91
		262	4·08	294	3·41
		364	4·23		
32[f] NH·C_6H_4Me-*m*	222	220	4·36	246	3·85
		(230)	4·28	304	3·44
		273	4·24		
		375	4·29		
33[a] NH·C_6H_4Me-*p*	242	222	4·33	246	3·90
		(234)	4·31	306	3·52
		274	4·28		
		378	4·30		
34[f] NH·C_6H_4·NO_2-*m*	256	230	4·37	246	4·14
		267	4·34	298	3·65
		360	4·33		
35[f] NH·C_6H_4·NO_2-*p*	280	227	4·42	286	3·43
		(245)	4·13		
		(337)	4·10		
		382	4·61		

[a] Specimen kindly supplied by Prof. Colonna. [b] Bogert and Corbitt, *J. Amer. Chem. Soc.*, 1926, **48**, 783. [c] Bogert and Taylor, *Chem. Abs.*, 1932, **26**, 1281. [d] Hofmann, *Ber.*, 1887, **20**, 1791. [e] Brooker *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 3192. [f] See p. 2264. [g] Illuminati and Gilman, *J. Amer. Chem. Soc.*, 1949, **71**, 3351. [h] Hofmann, *Ber.*, 1879, **12**, 1130. [i] Hunter and Jones, *J.*, 1930, 2190. Hasan, Hunter, and Firdaus, *J.*, 1936, 1672. [k] Drozdov and Stavroskaja, *Chem. Abs.*, 1940, **34**, 103.

* B. p.s of compounds as numbered were: (1) 95°/6 mm.; (2) 237°; (12) 183—187°/3 mm.; (13) 235—237°/17 mm.; (14) 245°/17 mm.

252 mμ (instead of 231 mμ). A third absorption, whose upper state may be derived from the benzene E_{1u} state, could be seen in the spectrum of benzoxazole only in the first onset, but in that of benzothiazole comes well into the observed spectral range with a maximum at 216 mμ.

These bathochromic shifts would be expected from the assignments suggested. In benzoxazole there is some conjugation between the oxygen $2p$ electrons and the benzenoid $2p\pi$ shell. In benzothiazole, for stereoelectronic reasons, somewhat weaker conjugation is expected between the sulphur $3p$ electrons and the carbon $2p\pi$ shell. These statements apply to the ground state. But in the B_{2u}-derived excited states, in which the $2p\pi$ shell is swollen, and also concentrated more over the atoms and less over the bond centres, sulphur conjugation gains a relative stereoelectronic advantage over oxygen conjugation, with the result that this upper state is depressed towards the ground state, with reduction in the transition energy, more in the sulphur than in the oxygen compound. Similar reasoning can be applied to the still higher states and transitions of the benzo-ring



chromophore. There seems to be no reason for expecting any substantial intensification, such as usually accompanies the more familiar bathochromic shifts due to extensions of conjugation.

2-Phenylbenzothiazole (Table 1, No. 3; Fig.).—As with benzoxazole, so with benzothiazole, the effect of a 2-phenyl substituent is to submerge the B_{2u}-like system, ascribed to the benzo-ring chromophore, in a much stronger, broad band of somewhat greater wave-length, while the shorter-wave part of the spectrum, containing the second and the third absorption assigned to the benzo-chromophore, remains almost unaffected by the substituent.

It is significant that, whereas in the shorter-wave absorptions of 2-phenylbenzothiazole, the already discussed bathochromic shifts, relatively to the spectrum of the oxygen analogue, are repeated, yet the long-wave band has an almost identical position and intensity in the two spectra (λ 297—299 mμ, log ε 4·3). This is consistent with its assignment to the different, nearly independent, benzylidene-imine chromophore.

Hydroxy-, Nitro-, Amino-, and Dimethylamino-derivatives of 2-Phenylbenzothiazole (Table 1, Nos. 4—10). Apart from general similarities and differences, such as have been illustrated above, the spectra of these substituted 2-arylbenzothiazoles are so similar to

those of the benzoxazole analogues that the analysis in the preceding paper may be considered to apply.

However, data are given for the hydroxy-compounds (cf. Table 1 of Part I), in confirmation of the theory of hydrogen-bonding in the *o*-hydroxyphenyl compounds with the hetero-nitrogen atom. If we had tried to set up the alternative hypothesis of conjugation with the hetero-oxygen atom, it could not have been carried over into the benzothiazole series, since hydrogen-bonding with thiazole sulphur is inconceivable, the unshared electrons of neutral sulphur (in any form) having no noticeable affinity for protons.

2-Methylthio-, 2-Arylthio-, and *2-Arylamino-benzothiazoles* (Table 1, Nos. 11—21).—The ultra-violet spectrum of 2-methylthiobenzothiazole has been described by Morton and Stubbs (*J.*, 1939, 1321), whose results agree with ours. The spectrum of 2-phenylthiobenzothiazole is closely similar. These spectra, and that of 2-anilinobenzothiazole, as well as the spectra of all the derivatives having methyl or nitro-groups in the 2-phenylthio- or 2-phenylamino-residue, are similar to the spectra of the corresponding benzoxazole compounds, apart from general differences, as already illustrated, and one further noteworthy difference. In general, then, the relevant discussion in the preceding paper may be considered to apply. The new point is that the long-wave absorption in the 2-thio-compounds, which was, and is, assigned to the introduced thioamide chromophore, is broader in the benzothiazole than in the benzoxazole series. Tentatively, we ascribe the broadening to a resonance, consequent on the presence of two identical atoms (sulphur) similarly involved in the thioamide (now dithiocarbamate) structure in the benzothiazole.

TABLE 2.

Benzothiazoles	M. p.	Formula	Found : N, %	Reqd. : N, %
2-*o*-Tolylthio-	— *	$C_{14}H_{11}NS$	5·45	5·4
2-*m*-Tolylthio-	— †	,,	5·5	5·4
2-*o*-Toluidino-	127°	$C_{14}H_{12}N_2S$	11·8	11·65
2-*m*-Toluidino-	124	,,	11·8	11·65
2-*m*-Nitroanilino-	190	$C_{13}H_9O_2N_3S$	15·6	15·5
6-Nitro-2-phenylthio-	104	$C_{13}H_8O_2N_2S$	9·9	9·7
6-Nitro-2-*o*-tolylthio-	102	$C_{14}H_{10}O_2N_2S_2$	9·4	9·3
6-Nitro-2-*m*-tolylthio-	134	,,	9·5	9·3
6-Nitro-2-*p*-tolylthio-	146	,,	9·5	9·3
6-Nitro-2-*m*-toluidino-	222	$C_{14}H_{11}O_2N_3S$	15·0	14·7

* B. p. 237°/17 mm. † B. p. 245°/17 mm.

6-Nitrobenzothiazole, and its 2-Methyl-, 2-Phenyl-, 2-Methylthio-, 2-Arylthio-, and 2-Arylamino-derivatives (Table 1, Nos. 22—35).—The importance of these spectra is that they confirm the rule, deduced in the preceding paper, that large separations between the longer- and shorter-wave absorptions appear when a 6-nitro-group is present simultaneously with an unsaturated 2-substituent, thus supporting the presumed locations of the chromophores by the observation of electronic splittings resulting from their overlap.

EXPERIMENTAL

The specimens measured were either obtained as noted in the references under Table 1, or prepared as here described. Except for 6-nitro-2-*m*-nitrophenylbenzothiazole, all the products detailed in Table 2 were obtained by heating under reflux equimolecular ethanolic solutions of 2-chloro- or 6-nitro-2-chloro-benzothiazole and the appropriate potassium mercaptide or aniline derivative. The products were purified by distillation under reduced pressure, or by crystallisation after evaporation of the ethanol.

For the preparation of *6-nitro-2-m-nitrophenylbenzothiazole*, equivalent amounts of 2-chloro-6-nitrobenzothiazole and *m*-nitroaniline were heated in an oil-bath at 160—190° for 2 hr. The product was crystallised, first from acetic acid, and then from nitrobenzene, forming yellow needles, m. p. 257° (Found : N, 17·8. $C_{13}H_8O_4N_4S$ requires N, 17·7%).

Light-absorption measurements were made as indicated in Part I.

The authors thank Professor M. Colonna for furnishing the spectral data for the first three compounds listed in Table 1 (cf. Fig.), and Professor C. K. Ingold, F.R.S., for helpful discussion of the spectroscopic data.

ISTITUTO DI CHIMICA INDUSTRIALE DELL' UNIVERSITA,
BOLOGNA.

[*Received, January 6th,* 1954.]

*Clovene and β-Caryophyllene Alcohol.**

By Albert W. Lutz and Evans B. Reid.

[Reprint Order No. 4902.]

Evidence is advanced to show that clovene, as ordinarily obtained, is a mixture of isomeric sesquiterpenes inseparable by distillation. Bromination of ordinary clovene yields a mixture of two stable isomeric dibromides which, upon fractional crystallisation, have yielded the first solid derivatives of this oily terpene. The oxidation of pure clovene furnishes clovenic acid in high yield, and additional evidence has been secured proving that clovene lacks hydrogen atoms alpha to the double bond.

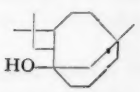
The reduction of clovenic acid furnishes a glycol that is extremely resistant to reagents that usually effect the *neo*pentyl rearrangement. Dehydration with potassium hydrogen sulphate gives, as the main product, a cyclic ether that is adamantine to ring fission and on oxidation furnishes a very stable lactone.

The carbon skeleton of pure clovene has been shown unequivocally to be identical with that of a tricyclic glycol, the structure of the latter being established by Barton and his co-workers.

Whilst β-caryophyllene alcohol would be expected to yield clovene on dehydration with Wagner–Meerwein rearrangement, and is so reported in the literature, this is shown conclusively not to be the case. Instead, a new structural isomer of clovene is obtained, termed *pseudo*clovene.

The tricyclic monounsaturated sesquiterpene, clovene, is reported to be formed from the dicyclic β-caryophyllene by a variety of methods. Using the Bertram–Walbaum reagent (glacial acetic and dilute sulphuric acids) Wallach and Walker (*Annalen*, 1892, **271**, 285) obtained the oily hydrocarbon (clovene) together with a solid tricyclic alcohol, $C_{15}H_{26}O$, β-caryophyllene alcohol. This extremely stable alcohol, boiling at 287—289° without decomposition, readily furnished the chloride, bromide, and iodide on treatment with the appropriate phosphorus halide, and from the chloride the corresponding acetate was obtained (Henderson, McCrone, and Robertson, *J.*, 1929, 1368). Because of its extreme resistance towards oxidising agents the alcohol was assumed to be tertiary in nature, with the hydroxyl group probably located on a bridge-head carbon atom. This assumption was supported by the observation that under very vigorous oxidising conditions the substance was drastically degraded to a liquid acid, $C_{10}H_{12}O_3$ (Bell and Henderson, *J.*, 1930, 1971). In addition, Wallach and Walker (*loc. cit.*), by dehydration of β-carypohyllene alcohol with phosphoric oxide, obtained a hydrocarbon, $C_{15}H_{24}$, b. p. 261—263°, n_D^{18} 1·50066, which they assumed to be clovene because of its similarity to the isomerisation product of β-caryophyllene. The fact that clovene, in their hands, failed to be capable of regenerating β-caryophyllene alcohol lent support to the assumption of a bridge-head hydroxyl group, and suggested that dehydration was only effected with concomitant structural rearrangement.

The recent *X*-ray crystallographic determination of β-caryophyllene aclohol chloride (Robertson and Todd, *Chem. and Ind.*, 1953, 437) not only confirmed the original deductions concerning the bridge-head structure of the alcohol, but established the structure (I) and stereochemistry of the molecule as well.



(I)

By a modification of the above dehydration process Henderson, McCrone, and Robertson (*loc. cit.*) obtained a mixture of sesquiterpenes which were separated into (1) a compound thought to be clovene, b. p. 111—113°/10 mm., n_D^{20} 1·4980, and (2) another oil, termed *iso*clovene, b. p. 130—131°/12 mm., α_D^{14} −56·6°.

Dehydrohalogenation of caryophyllene dihydrochloride by quinoline or pyridine (Semmler and Mayer, *Ber.*, 1910, **43**, 3451) afforded a tricyclic sesquiterpene, b. p. 122—123°/13 mm., n_D^{20} 1·50246, α_D^{20} −57°, which it has been suggested is identical with clovene (Henderson, McCrone, and Robertson, *loc. cit.*; Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 66). A liquid monohydrochloride of caryo-

* Much of the material presented in this paper has been described previously in abbreviated form (*Chem and Ind.*, 1953, 278, 749).

phyllene gave, on treatment with silver acetate in acetic acid, an oil, b. p. 118—124°/10 mm., n_D^{20} 1·4992, also considered to be clovene (Bell and Henderson, *loc. cit.*), together with the acetate of a tricyclic alcohol which when hydrolysed and dehydrated furnished an olefin, n_D^{17} 1·5004, likewise considered to be clovene.

The work of Asahina and Tsukamoto (*J. Pharm. Soc. Japan*, 1922, **463**) showed that hydration of caryophyllene with Aschan's reagent (sulphuric acid monohydrate in ether) furnished, not only a mixture of clovene and β-caryophyllene alcohol, but also α-caryophyllene alcohol, m. p. 117°. The last, on dehydration with phosphoric anhydride (Bell and Henderson, *loc. cit.*) yielded clovene, b. p. 118—123°/12 mm., n_D^{17} 1·5000.

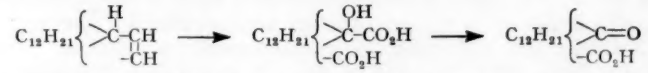
It is apparent, from the variations in the physical constants reported, that clovene has never been adequately characterised and that, owing to the lack of solid derivatives, no satisfactory criterion for either the purity or the identity of the terpene is available except its degradation to the dicyclic dibasic clovenic acid (Ruzicka and Gibson, *Helv. Chim. Acta*, 1931, **14**, 575). This acid, while of use for identification, cannot be used for the regeneration of pure clovene. It should also be pointed out that the yields of clovenic acid reported in the older literature have not exceeded 40%.

In our work with clovene it was considered essential to obtain pure material. Commercial caryophyllene from two sources was freed from traces of phenolic impurities by treatment with alkali. Hydration with Aschan's reagent furnished the expected β-caryophyllene alcohol and crude clovene, together with very low yields of α-caryophyllene alcohol, and a new hydration product, $C_{15}H_{26}O$, m. p. 70—71°. In most of our work, isolation was accomplished by using superheated steam (about 160°), and under these conditions no α-caryophyllene alcohol was obtained. It seems justified to conclude, therefore, that at the higher isolation temperature α-caryophyllene alcohol is completely dehydrated to clovene.

Fractional distillation of this crude clovene through an efficient column gave fractions boiling from 114·5° to 128·5° at 12·0 mm., with $\alpha_D^{25\cdot0}$ varying from −20·24° to −54·21°. An infra-red absorption spectrum of an intermediate fraction proved identical with one later reported by Eschenmoser and Günthard (*Helv. Chim. Acta*, 1951, **34**, 2338) for their clovene purified by distillation.

Bromination of clovene (purified by distillation) gave, in relatively poor yield, a solid mixture of isomeric dibromides that was distillable *in vacuo* (b. p. 153—162°/1·0 mm.) with only slight decomposition. Fractional crystallisation from ethanol furnished the major isomeride, m. p. 71·0—71·5°, and the minor isomeride, m. p. 41—43°. These appeared be the first crystalline derivatives to have been prepared from clovene, and very pure specimens of clovene (b. p. 115·0°/12·5 mm., $n_D^{25\cdot0}$ 1·4913, $\alpha_D^{25\cdot0}$ −23·37°) were regenerated from each dibromide by extended treatment with zinc dust. It is of significance that the bromine atoms in these isomerides are extremely inert. Thus, treatment of either dibromide with refluxing alcoholic potassium hydroxide for 3 hours was without effect, and in boiling ethanol solution the action of zinc dust was only slight after 3 hours. Also of significance is that our very pure clovene furnished, on oxidation, clovenic acid in high yield. In this connection we also satisfied ourselves that the formation of clovenic acid proceeded without skeletal rearrangement (cf. Byers and Hickinbottom, *J.*, 1948, 1334), for the crystalline acid was formed by oxidation with chromic acid, alkaline permanganate (very slowly), or by the action of ozone followed by hydrogenation and then oxidation.

It was observed in our work with clovene purified only by distillation, that oxidation by several reagents gave clovenic acid together with two acidic by-products. One of these, after purification through its methyl ester, had the empirical formula $C_{14}H_{22}O_3$ and proved to be a monocarboxylic keto-acid. On the other hand, our very pure clovene gave none of this by-product, indicating that clovene, as ordinarily obtained, contains as an impurity an isomeric hydrocarbon possessing the partial structure :



and that the course of its oxidation is as suggested in the above sequence. All efforts to obtain a crystalline derivative of the keto-acid were without success.

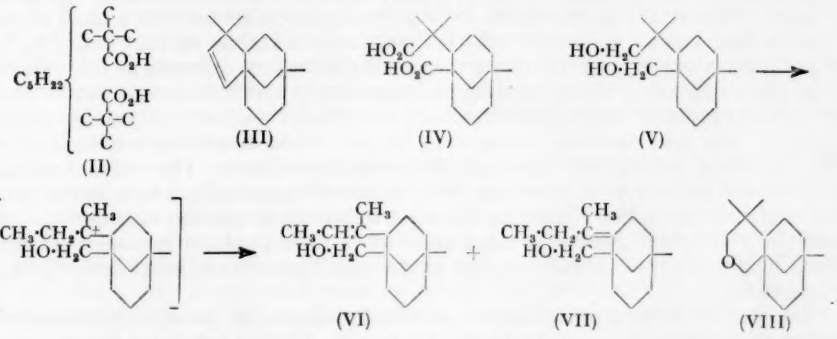
The second acidic by-product, obtained only in small quantities, had m. p. 101—102° and the formula $C_{12}H_{20}O_3$. It is presumed that this acid is also derived from the impurity in clovene. The acid was unstable, giving neutralisation equivalents that varied according to the method of determination. Paucity of material prevented further experimentation.

The neutral fraction, obtained from the oxidation of ordinary clovene with chromic anhydride, amounted to about 24% (by weight), and was investigated briefly. It contained mainly unchanged clovene, together with a high-boiling ketone, analysis of whose 2 : 4-dinitrophenylhydrazone showed it to be an unsaturated tricyclic monoketone, $C_{15}H_{22}O$.

In the Wohl–Ziegler reaction, ordinary clovene reacted very sluggishly and incompletely with *N*-bromosuccinimide. Isolation, *via* short-path distillation, furnished a dark yellow product, unstable unless kept under nitrogen at solid carbon dioxide temperature. This material gave very low analyses for bromine, and it was concluded that clovene probably contained no hydrogen atoms alpha to the double bond, and our attention turned to clovenic acid as a starting point for degradative work.

The failure of clovenic acid to give the diagnostic test characteristic of tertiary acids (Bistrzycki and Mauron, *Ber.*, 1907, **40**, 4370), owing to preferential anhydride formation, while not conclusive, was strongly indicative of the presence of two tertiary acid groupings, and this was confirmed as follows. Attempts to prepare the di-acid chloride by interaction with oxalyl chloride (Adams and Ulrich, *J. Amer. Chem. Soc.*, 1920, **42**, 599), a process that normally is successful with either dicarboxylic acids or their anhydrides, gave only clovenic anhydride. Attempted ammonolysis with gaseous ammonia on dimethyl clovenate in alcohol for 18 days resulted in only unchanged ester. Application of the Schmidt reaction (" Organic Reactions," John Wiley and Sons, New York, 1st Edn., p. 307), using the modification wherein clovenic acid and hydrazoic acid in benzene were treated with sulphuric acid dropwise (cf. Blair, *J.*, 1935, 1297), yielded only clovenic anhydride. The above experiments, when considered in conjunction with the stability of the acid towards nitric acid and other oxidising agents (Blair, *loc. cit.*) and towards isomerising conditions (Barton, Bruun, and Lindsey, *J.*, 1952, 2210), together with the facts that the acid resists bromination and ketonisation (Ruzicka and Gibson, *loc. cit.*), can only be accommodated by a di*neo*-pentyl system, as in (II).

Reduction of clovenic acid to the corresponding glycol (V) should thus furnish a structure containing two *neo*pentyl groupings. In view of the work by the Whitmore school (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1932, **54**, 22, 3274, 3431, 3435, 4011; 1933, **55**, 1119, 3721, 4161; cf. Ingold, *J.*, 1923, **123**, 1706) on rearrangements in the *neo*pentyl system, it seemed reasonable to expect that an analogous rearrangement by the glycol, with concomitant dehydration, should give unsaturated products of predictable structures, amenable to degradation. Thus, if expression (III) is adopted for clovene (Barton, Bruun, and Lindsey, *Chem. and Ind.*, 1951, 1910; *J.*, *loc. cit.*; Eschenmoser and Günthard, *loc. cit.*), reduction of



clovenic acid (IV), should yield the glycol (V), which on dehydration would be expected to furnish a mixture of olefins (VI and VII). It may be noted that the second carbinol grouping, since located on the bridge-head, would not be expected to be involved in the dehydra-

tion with rearrangement, since the requisite ring expansion from C_6 to C_7 would locate the positive charge at the bridge-head, and stabilisation *via* proton expulsion would result in formation of an ethylenic bond at the bridge-head of a system wherein *S* is less than ten (cf. Fawcett, *Chem. Reviews*, 1950, **47**, 219).

Lithium aluminium hydride reduction of either dimethyl clovenate or clovenic acid resulted in the smooth formation of a gummy, hygroscopic, immobile oil that was characterised through its crystalline diphthalate. On dehydration with fused potassium hydrogen sulphate one molecule of water was lost, with formation in good yield of a substance of m. p. 12·5°. Quantitative hydrogenation and acetylation, and semiquantitative bromination studies, proved this to contain about 10% of unsaturated alcohol, the rest being inert ethereal material that showed in the infra-red a strong absorption at 9·0 μ (1111 cm.$^{-1}$) (ether absorption). It is thus apparent that dehydration mainly proceeded to form the cyclic ether (VIII) (compare the ready dehydration of clovenic acid), there being very little of the hoped-for dehydration with rearrangement.

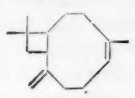
Oxidation of the above mixture of dehydration products with potassium permanganate in pyridine furnished a degraded keto-dicarboxylic acid, $C_{13}H_{20}O_5$, m. p. 178·5—180° (depressed to 149—150° on admixture with clovenic acid), in low yield, together with the main product, a neutral material, m. p. 93·0—94·5°, $C_{15}H_{24}O_2$. The latter was completely inert to basic hydrolysis, bromination, and oxidation, and showed no carbonyl reactions, behaviour reminiscent of that of the presumed lactone obtained by treatment of clovenic anhydride with phenylmagnesium bromide (Blair, *loc. cit.*). The lactonic structure of our product was confirmed by a strong absorption band at 5·88 μ (1700 cm.$^{-1}$) in the infra-red (oil paste).

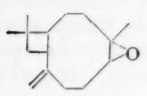
Whilst analogy for lactone formation from a cyclic ether is found in the catalysed air-oxidation of tetrahydrofuran and tetrahydropyran to γ-butyrolactone and δ-valerolactone, respectively (Bremmer and Jones, B.P. 608,539, 1948), the extreme stability of our product must be due to steric reasons. The compound was completely stable to excess of refluxing hydrobromic–sulphuric acid for 30 hours, and was unaffected by chromic anhydride. It is of interest that the same keto-dicarboxylic acid, which is obviously derived from the unsaturated alcohol, and the lactone were obtained by treatment of the dehydration mixture with ozone, followed by chromic acid.

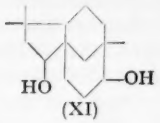
It unfortunately proved impossible to establish dehydration conditions that would furnish workable yields of rearranged dehydration products. Thus, concentrated sulphuric–toluene-*p*-sulphonic acid mixture gave, as the major product, a low-boiling material, $C_{15}H_{26}O$; this was a mixture of saturated and unsaturated components differing from those produced by potassium hydrogen sulphate, for on oxidation with potassium permanganate a very low yield of a diketo-dibasic acid, $C_{15}H_{24}O_6$, was obtained, together with a large neutral fraction that gave negative carbonyl and glycol tests. Oxidation of the mixture with chromic acid yielded a trace of a dibasic keto-acid, $C_{14}H_{22}O_5$, and a quantity of neutral material shown to be starting product mixed with a small amount of higher-boiling ketonic substance. With formic acid, a mobile oil (22%), $C_{15}H_{26}O$, was formed, the major (78%) fraction being the monoformate ester of clovene glycol. Oxidation of the minor component with potassium permanganate in pyridine formed a neutral product, saturated to bromine, that failed to respond to carbonyl reagents. A trace of solid acid, $C_{15}H_{24}O_6$, was also obtained, thought to be the diketo-dibasic acid mentioned above although mixed melting point determinations were inconclusive. The action of phosphoric oxide seemed initially more promising, for a mixture of saturated and unsaturated products was obtained, the latter containing material shown to be doubly unsaturated. Unfortunately, attempts to isolate the small amounts of these products in pure state by fractional distillation, or chromatography, or through formation of solid derivatives, were unsuccessful.

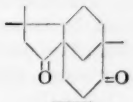
Evidence for the Structure of Clovene, and the Dehydration of β-Caryophyllene Alcohol.—Earlier work in these laboratories by Mr. Norman W. Atwater had shown that β-caryophyllene (IX) was cyclised by performic acid to a tricyclic glycol, both of whose hydroxyl groups were secondary since on oxidation a diketone was formed, characterised through its bis-2 : 4-dinitrophenylhydrazone. The same glycol (direct comparison through the

courtesy of Professor D. H. R. Barton) had been prepared independently (Barton, personal communication; Aebi, Barton, and Lindsey, *Chem. and Ind.*, 1953, 748) by mild acid hydrolysis of β-caroyphyllene oxide (X). These authors established the probable structure of the glycol as (XI) originating *via* a logical mechanistic route from the oxide, and the diketone as (XII), with the supporting evidence of infra-red absorption data for five- and six-ring ketones. Finally, in an elegant series of reactions, they transformed the diketone (XII), into clovenic acid (IV). The relation of the carbon skeleton of the glycol, and its derived diketone, to that postulated for clovene (III) is obvious. We have therefore transformed both the diketone (XII) and clovene into a common structure, clovane, by quantitatively hydrogenating clovene and, in 76% yield, by Wolff–Kishner reduction of the diketone (XII).*


(IX)


(X)


(XI)


(XII)

(XIII)

(XIV)

(XV)

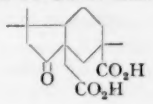
(XVI)

The above transformations, when considered in conjunction with the ultimate degradation of the glycol (XI) to clovenic acid (Aebi, Barton, and Lindsey, *loc. cit.*) unequivocally establishes the same carbon skeleton in clovene as in the glycol, and the structure of the latter cannot reasonably be doubted. If structure (III) is accepted for clovene, a direct relation should exist between clovene and β-caryophyllene alcohol (I), since dehydration with Wagner–Meerwein rearrangement of the latter would be expected to furnish the hydrocarbon. Indeed, the literature contains statements in support of this dehydration (Wallach and Walker; Henderson, McCrone, and Robertson, *locc. cit.*). Careful repetition of this dehydration (phosphoric oxide) has shown, however, that while the product closely resembles clovene in so far as its boiling point and refractive index are concerned, its rotation is of opposite sign, its infra-red absorption spectrum shows distinct differences, and its chemical behaviour is completely different. Thus, in contradistinction to clovene, the new dehydration product, which we have termed *pseudo*clovene, forms an unstable compound with bromine and on oxidation forms an oily dibasic acid isomeric with clovenic acid. Although clovenic acid is ditertiary, *pseudo*clovenic acid must contain α-hydrogen atoms, for it undergoes ready substitution in the Hell–Volhard–Zelinski reaction, forming a dibromo-acid that was characterised through its dimethyl ester. Further, *pseudo*clovene must contain hydrogen atoms alpha to the double bond, for, unlike clovene, it reacted smoothly with *N*-bromosuccinimide to form an unstable bromo-derivative.

Clovene and *pseudo*clovene must therefore be structural isomers. The number of dehydration products (without rearrangement) resulting from (I) is strictly limited, and on the basis of the evidence at hand, formula (XIV) is tentatively proposed for *pseudo*clovene, and (XV) for *pseudo*clovenic acid.

The question naturally arises of the rôle of β-caryophyllene alcohol in the formation of clovene from β-caryophyllene. The alcohol was recovered unchanged when treated with Aschan's reagent under the conditions used in the preparation of clovene, or with boiling 20% sulphuric acid for 4½ hours. However use of much more vigorous conditions than obtain for the hydration of β-caryophyllene, *i.e.*, in ether–concentrated sulphuric acid at 75° for 1 hour, gave a mixture of an unsaturated hydrocarbon (25%), not clovene, and a saturated hydrocarbon (75%). The formation of the latter is reminiscent of Oddo and

* During the oxidation of the glycol to the diketone a small amount of acidic material was obtained as a by-product, apparently the annexed keto-dicarboxylic acid; it results from oxidation of the diketone (cf. Aebi, Barton and Lindsey, *loc. cit.*).



Scandola's reduction (*Gazzetta*, 1909, II, **39**, 44) of several alcohols to alkanes by sulphuric acid. In our case ether–sulphuric acid was used, and preliminary cleavage of the ether to ethanol would furnish a readily oxidisable component. The structure of our saturated hydrocarbon must be (XVI), for oxidation of the hydrocarbon mixture with chromic acid resulted in the formation of β-caryophyllene alcohol, together with a small amount of a keto-acid, $C_{13}H_{22}O_3$, that formed an oily 2 : 4-dinitrophenylhydrazone and gave a methyl ester that did not undergo the haloform reaction. The formation of β-caryophyllene alcohol in this reaction was shown to be due to oxidation and not to hydration of a double bond (which would have to be located at the bridge-head), since the same reaction conditions, but without the oxidant, failed to yield the alcohol.

It thus is established that despite the logical structural relation between β-caryophyllene alcohol and clovene, it is not possible to effect the transformation in the laboratory. From this it must be concluded that the hydration of β-caryophyllene with Aschan's reagent takes at least two paths : in one the relatively stable β-caryophyllene alcohol is formed ; in the other, clovene and other products are produced. It also seems certain that these two paths are mutually exclusive and presumably involve different ionic intermediates.

Experimental

Some of the analyses are by Mr. J. Walter, The John Hopkins University.

Clovene.—As a result of many comparative experiments, the procedure of Asahina and Tsukamoto (*loc. cit.*) was modified as follows. Concentrated sulphuric acid (900 g.) was added dropwise to ether (1700 ml.) in a 12-l. flask at 0°. To this solution was added 3 kg. of commercial caryophyllene (Dodge and Olcott, New York ; previously extracted with dilute aqueous sodium hydroxide) at such a rate that the temperature remained below 10°. The mixture was kept overnight and then neutralised by the slow addition of technical sodium hydroxide flakes (600 g.) in 20% aqueous solution, after which solid sodium hydroxide (600 g.) was added carefully. Water was added occasionally, so that the final volume was about 9 l. The use of sodium hydroxide eliminated the excessive frothing that occurs if the recommended sodium carbonate is used. The final mixture, in two portions, was exhaustively distilled in steam pre-heated to 160°. The distillate was separated crudely into 1082 g. of solid and 1477 g. of oil. Recrystallisation of the solid from acetone gave pure β-caryophyllene alcohol, micro-m. p. 96·5—97° (Kofler hot stage).

Re-acidification of the distillation residue followed by exhaustive steam-distillation failed to furnish additional products. However, when steam-distillation at 100° was used, besides β-caryophyllene alcohol and clovene, a small amount of α-caryophyllene alcohol was obtained, having m. p. 118—119° (from acetone), together with a small amount of new hydration *product*, m. p. 70—71° (from acetone), isomeric with the caryophyllene alcohols (Found : C, 81·1 ; H, 11·7. $C_{15}H_{26}O$ requires C, 81·0 ; H, 11·8%).

Clovene from Florasynth Laboratories gave similar results.

Purification of Clovene by Distillation.—Crude clovene (1 l.) was combined with benzene (300 ml.) and dried by distillation of the benzene–water azeotrope at atmospheric pressure. The residue was then distilled under nitrogen through a 48-in. adiabatically jacketed Stedman column equipped with conical-type packing. At 12·0 mm., and with the column operating continuously for 24 hr., nine fractions were taken whose constants varied between the limits, b. p. 114·5—128·5°, $\alpha_D^{25\cdot0}$ −20·24° to −54·21°, $n_D^{25\cdot0}$ 1·4908—1·5032. Fractions 1—7 were combined (558·5 g.) and redistilled through the Stedman column, with arbitrary 25-ml. fractions, giving the tabulated fractions :

Fraction	B. p./12 mm.	$\alpha_D^{25\cdot0}$	$n_D^{25\cdot0}$
1	114·5—114·8°	−19·50°	1·4895
2—9	114·9—116·0	−20·21 to −21·20	1·4094—1·4912
10—12	116·0—116·0	−21·60 to −22·54	1·4925—1·4925
13—23	116·0—118·5	−22·85 to −38·17	1·4924—1·4910
24—25	119·3—120·5	−47·06 to −50·28	1·4901—1·4895

An infra-red absorption spectrum of fraction 6, b. p. 115·4°/12·0 mm., $\alpha_D^{25\cdot0}$ −20·80°, $n_D^{25\cdot0}$ 1·4909, was identical with that reported by Eschenmoser and Günthard (*loc. cit.*) for their pure clovene.

Purification of Clovene through the Dibromide.—Distilled clovene (30 g.) in carbon tetrachloride (200 ml.) was chilled to 0° and bromine (24 g.) in carbon tetrachloride (100 ml.) was

added dropwise and with stirring during 12 hr. (temperature kept at 0°). The light yellow solution was allowed to warm to room temperature, was stirred for an additional 6 hr., washed with 5% bicarbonate solution and then water to neutrality, dried (Na_2SO_4), and evaporated *in vacuo*. The residue (32 g.) crystallised spontaneously. Fractional crystallisation from 95% ethanol gave a *dibromide* (38% of the crude product), m. p. 71·0—71·5° (Found: C, 49·65; H, 6·7. $C_{15}H_{24}Br_2$ requires C, 49·45; H, 6·65%), and an *isomer* (23%), m. p. 41—43° (Found: C, 49·4; H, 6·6%). Gravimetric bromine analyses were unsuccessful, since the compounds were not attacked by boiling alcoholic potassium hydroxide. The residue from the above crystallisation had m. p. 44—65°, and was not further separated.

Regeneration of Clovene.—The high-melting dibromide (21·0 g.) in 95% ethanol (300 ml.) was refluxed with zinc dust (8·7 g.) for 8 hr. The mixture was then poured into water and extracted with ether four times. The troublesome emulsion that formed was dispelled by making the aqueous layer slightly acidic. The extracts were washed with water until free from halide ion and dried (Na_2SO_4). After evaporation, the residual oil was fractionated through a short column and gave one fraction of colourless oil, b. p. 115·0°/12·5 mm., $n_D^{25·0}$ 1·4913, $\alpha_D^{25·0}$ −23·37°. The yield was 9·07 g. (77%) of pure *clovene* (Found: C, 88·3; H, 12·0. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%).

Similar treatment of the low-melting dibromide gave clovene, b. p. 111—112°/11·5 mm., $n_D^{25·0}$ 1·4902, $[\alpha]_D^{27·0}$ −27·1° (in $CHCl_3$; *c* 3·13).

The Wohl–Ziegler Reaction.—Clovene, purified only by distillation (40 g.), was dissolved in carbon tetrachloride (200 ml.), and *N*-bromosuccinimide (35 g., 1 equiv.) was added. The mixture was refluxed for 16 hr. under infra-red radiation, at which point the reaction was complete. A portion of the product was distilled from a Hickman short-path still at 10^{-3} mm., to give two fractions. The first contained only 3·5% of bromine. The second (bath-temp. 50°) contained 10·7% (Calc. for $C_{15}H_{23}Br$: Br, 28·2%). Unless stored under nitrogen at −80°, the product decomposed. Unsuccessful attempts were made to free the bromide from contaminants *via* the β-naphthyl ether and the *S*-alkyl*iso*thiourea picrate.

Oxidations of Clovene.—(1) Ordinary clovene in carbon tetrachloride was oxidised with potassium permanganate while a stream of carbon dioxide was conducted through the mixture. After the usual working up, a 7·2% yield of pure clovenic acid was obtained together with 79·5% of neutral (starting) material.

(2) Treatment of ordinary clovene in ethyl acetate solution with ozone for 10 hr. at 0° was followed by reduction of the ozonide with hydrogen and 2% palladised calcium carbonate (49·6% of theoretical H_2 uptake). The thick residual oil was then oxidised with permanganate, yielding clovenic acid in 47% yield.

(3) Ordinary clovene was ozonised in methylene chloride (cf. Henne and Hill, *J. Amer. Chem. Soc.*, 1943, **65**, 752), then oxidised with hydrogen peroxide and finally permanganate. Clovenic acid was obtained in 41% yield.

(4) With chromium trioxide (Ruzicka and Gibson, *loc. cit.*) ordinary clovene formed clovenic acid in 51·5% yield.

(5) With clovene purified through the dibromide, chromium trioxide oxidation furnished the acid in 75% yield, the residue being unchanged hydrocarbon.

$C_{14}H_{22}O_3$ *Keto-acid.*—The acidic product (64 g.) obtained from the chromium trioxide oxidation of ordinary clovene was triturated in two portions (200 ml.) of acetone, to give 36 g. of white insoluble clovenic acid, m. p. 166—170°. Concentration of the acetone solution furnished an additional 3·2 g. of clovenic acid, and complete removal of the solvent left 25 g. of oily acid (61 parts of clovenic acid to 39 of oily keto-acid). The oily acid (25 g.) was refluxed for 24 hr. with methanol (25 ml.) and mixed alkanesulphonic acids (3 ml.) in chloroform (270 ml.), with anhydrous magnesium sulphate (Soxhlet) to remove the water formed. This gave 26·6 g. (96·4%) of crude ester that was fractionated through a 32 cm. Vigreux column and yielded the pure *methyl ester*, b. p. 123·5°, $n_D^{25·0}$ 1·4800 (Found: C, 71·5; H, 9·5%; sap. equiv., 252·9. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%; sap. equiv., 252·4). Both the keto-acid and its methyl ester with 2 : 4-dinitrophenylhydrazine reagent readily formed yellow oils that darkened on storage. The oils could not be induced to crystallise, even after chromatographic purification. A variety of derivatives was tried unsuccessfully including the semioxamazide, *p*-phenylphenacyl ester, benzylamine salt, benzylamide, *p*-bromoanilide, and anilide.

On one occasion the crude, oily, acidic portion (from the acetone mull) was kept for several days dissolved in a minimum amount of light petroleum, while 2—3 g. of solid separated. The *substance* was very soluble in the usual organic solvents, but furnished white glistening needles [from ethanol–water (6 : 4)], m. p. 101—102° (Found: C, 68·3; H, 9·3. $C_{12}H_{20}O_3$ requires

C, 67·9; H, 9·5%); the neutralisation equivalent was: (1) dissolved in base and immediately titrated, 318; (2) dissolved in warm base, titrated after 15 min., 261; (3) in warm base after 2·5 hr., 248; (4) refluxed in base for 13 hr., 166. On storage at room temperature, the substance lost its lustre and crumbled, and then had m. p. 58—70°.

Neutral Fraction from Clovene Oxidation.—The neutral material (63 g.) resulting from several oxidations of ordinary clovene with chromium trioxide was fractionated to give, along with much unchanged clovene, a fraction, b. p. 116—130°/1·3 mm., that contained ketonic material (20 g.). This was redistilled at 1·2 mm., and a fraction, b. p. 110·5—115°, $n_D^{25\cdot0}$ 1·5039, was taken (5·6 g.). The ketone formed an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 194—196° (from methanol) (Found: C, 63·3; H, 6·4; N, 14·0. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·6; N, 14·1%).

Clovenic Glycol.—Lithium aluminium hydride (49 g.) was slurried with absolute ether (2 l.) in a 5-l. flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping funnel. The dropping funnel contained powdered clovenic acid (76 g.) and anhydrous ether (500 ml.). The acid was kept in suspension by constant stirring, and the mixture was added to the reductant as fast as the reaction permitted. A second charge of clovenic acid (76 g.) in ether (500 ml.) was then added, and the mixture was refluxed for 34 hr. The excess of lithium aluminium hydride was then decomposed cautiously with water, and the whole acidified with 10% sulphuric acid. The ether layer was separated, the water layer was extracted twice with ether, and the combined ethereal extracts were washed several times with saturated sodium hydrogen carbonate solution, and then water. After drying and evaporation, a colourless gum remained. A portion of this *clovenic glycol* was distilled with great difficulty owing to the immobility of the substance, b. p. 140—142°/0·10 mm., $n_D^{25\cdot0}$ 1·5108 (Found: C, 74·7; H, 11·6. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·7%). The *diphthalate* was prepared by refluxing the glycol (0·5 g.) with phthalic anhydride (0·8 g.) in toluene (5 ml.) for 12 hr., and chilling the reaction mixture; it had m. p. 184—185° (from ethyl acetate) (Found: C, 69·4; H, 7·0. $C_{31}H_{36}O_8$ requires C, 69·4; H, 6·8%).

Potassium Hydrogen Sulphate Dehydration of Clovenic Glycol.—The glycol (25 g.) was mixed with finely ground, freshly fused potassium hydrogen sulphate (75 g.) in a distillation flask and slowly heated under a pressure of 0·25 mm. A vigorous reaction ensued as water vaporised from the flask, and then a colourless mobile oil distilled at 90°. The yield of crude product was 20·6 g., or 89%. After being washed with bicarbonate solution, water, and dried in ethereal solution, the product was distilled through a 17-cm. Vigreux column and the main fraction, b. p. 92—97°/0·20 mm., was taken (15·1 g.). Refractionation of this gave the monodehydrated product, mainly *clovenic ether*. b. p. 95·5°/0·20 mm., m. p. 12·5°, $n_D^{25\cdot0}$ 1·4970 (Found: C, 81·3; H, 12·1. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%). Microhydrogenation, semiquantitative bromination, and acetylation proved the product to be inhomogeneous and to consist of about 10% of unsaturated alcohol mixed with 90% of inert ethereal material.

Oxidation of the Dehydration Mixture.—The oil (5 g.) in pyridine (35 ml.) and water (10 ml.) was warmed on the steam-bath while powdered potassium permanganate (9·5 g.) was added in portions. After 3 hr. the purple solution was diluted with water (100 ml.), and the excess of oxidant reduced with sulphur dioxide. After extraction of the solution with ether, the extract was washed several times with dilute hydrochloric acid, and then dilute potassium hydroxide. After drying, evaporation of the ether gave a yellow mobile oil (4·2 g.), which partly solidified. The solid, *clovenic lactone* recrystallised from light petroleum as white prisms, m. p. 93·0—94·5° (Found: C, 76·45; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%). The lactone was inert to boiling 15% potassium hydroxide solution, and to chromium trioxide in acetic acid for 42 hr.

Distillation of the neutral oil (from which the lactone had solidified) revealed it to be mainly unchanged clovenic ether.

The acidic constituent (0·4 g.) from the above oxidation (obtained from the potassium hydroxide washings) was recrystallised from hexane–ethanol, to give fibrous needles of a *keto-dicarboxylic acid*, m. p. 178·5—180·0° (Found: C, 60·9; H, 7·8; equiv., 136·7. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·9%; equiv., 128·2).

Dehydration by Sulphuric Acid.—Clovenic glycol (6·8 g.) was mixed with concentrated sulphuric acid (0·82 g., or 12% by wt.), and toluene-*p*-sulphonic acid (0·55 g., 8% by wt.) in 15 ml. of toluene, and refluxed for 15 hr. The dark product was neutralised with carbonate solution, and the aqueous layer was extracted with toluene. After washing with water and drying, evaporation *in vacuo* gave 6·3 g. of dark brown mobile oil. Careful fractional distillation (Vigreux column) at 2·5 mm., gave a colourless product (2·5 g.), b. p. 113—114·5°, $n_D^{25\cdot0}$ 1·4964. A specimen of this monodehydrated *product* had b. p. 114°, $n_D^{25\cdot0}$ 1·4980 (Found: C, 81·2; H, 11·6. $C_{15}H_{26}O$ requires, C, 81·0; H, 11·8%). Microhydrogenation and quantitative

bromination revealed the presence of 19% of an unsaturated constituent, the remainder being a saturated compound *not* identical with clovenic ether since oxidation with permanganate in pyridine gave as the main product a neutral light oil that refused to crystallise, together with a *diketo-dicarboxylic aicd*, whose m. p. (from ethyl acetate) was not reproducible (234—235° up to 249—251°; Fisher–Johns m. p. block) [Found: C, 59·9; H, 8·0%; *M* (Rast), 292; equiv., 148. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·1%; *M*, 300; equiv., 150].

A portion (4·47 g.) of the above dehydration mixture was treated with chromium trioxide (5·4 g.) in acetic acid (25 ml.) (containing a little water) at 40° for 27 hr. and set aside for 4 days. This yielded mainly neutral material containing starting material, together with a trace of a ketone that furnished a solid 2 : 4-dinitrophenylhydrazone in microscopic quantities. A solid degraded *keto-dicarboxylic acid* (0·47 g.) was also formed, having m. p. 212·5—213·5° (from ethyl acetate) (Found: C, 61·9; H, 8·2%; equiv., 135. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%; equiv., 135).

Dehydration with Formic Acid.—Clovenic glycol (33 g.) was refluxed for about 7 hr. with 90% formic acid (300 ml.). After the usual working up there was obtained a monodehydration *product* (5·2 g.), b. p. 93—94°/1·2 mm., $n_D^{25·0}$ 1·4941 (Found: C, 81·4; H, 11·4. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%), together with *clovenic glycol monoformate* (22 g.), b. p. 138°/0·7 mm., $n_D^{25·0}$ 1·4989 (Found: C, 72·3; H, 9·95. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%). Hydrolysis of the monoformate with hot 10% aqueous sodium hydroxide readily yielded clovenic glycol, identified through the diphthalate.

Oxidation of the monodehydration product (2·0 g.) with potassium permanganate (3·8 g.) in pyridine (60 ml.) at 50° for 24 hr. yielded a thin neutral oil (1·15 g.), saturated to bromine and inert to 2 : 4-dinitrophenylhydrazine and to boiling 20% aqueous sodium hydroxide, together with a trace of *diketo-dicarboxylic acid*, prisms (from ethyl acetate), m. p. variable, 243—244°, 245—247° (Found: C, 59·8; H, 8·1. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·1%). A mixed m.p. of this acid with the above diketo-dicarboxylic acid was 236—237°.

Dehydration with Phosphoric Oxide.—Clovenic glycol (15 g.) was warmed to 50° and phosphoric oxide (13 g.) added portionwise while the temperature of the reactants rose to 100°, despite ice-cooling. After the usual working-up the crude product (10·4 g.) was fractionated (Vigreux column) at 4 mm., to yield a fraction, b. p. 105—107°, $n_D^{25·0}$ 1·4955 (0·45 g.), which contained mainly doubly unsaturated material (carbon and hydrogen total, 97·3%), although this could not be obtained pure. Bromination formed an unstable bromide. The main fraction (3·41 g.) had b. p. 108—122°/4 mm., $n_D^{25·0}$ 1·5001, and on oxidation with chromium trioxide gave largely neutral products that were not further studied.

Clovane (XIII).—Pure clovene (4·3 g.), obtained from clovene dibromide (m. p. 71·0—71·5°), was hydrogenated at 1 atm. in glacial acetic acid (20 ml.) with Adams catalyst (50 mg.) (uptake 99·3%). Fractional distillation at 12 mm. gave *clovane* as the only fraction, b. p. 115°, $n_D^{25·0}$ 1·4863, $[\alpha]_D^{26·0}$ −5·1° (in $CHCl_3$; *c* 5·13) (Found: C, 87·4; H, 12·7. $C_{15}H_{26}$ requires C, 87·3; H, 12·7%).

The $C_{15}H_{26}O_2$ *Glycol* (XI).—Caryophyllene (100 g.) was added dropwise to a stirred mixture of 90% formic acid (750 ml.) and 30% hydrogen peroxide (150 ml.) at such a rate that the temperature remained at 40—50° (5 hr.). Then the clear yellow solution was kept at 40° for an additional hour, and at room temperature for 4 hr. The formic acid was removed *in vacuo*, and the residue refluxed for 9 hr. with 10% sodium hydroxide solution, and then steam-distilled until 10 l. of distillate had formed. The non-volatile residue was taken up in ether, washed, treated with charcoal, and evaporated to a gum. Crystallisation from the minimum amount of ethyl acetate gave 25 g. of crude glycol; several recrystallisations from benzene furnished 16·5 g. of pure 4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{1,5}$]*dodecane*-2 : 9-*diol*, m. p. 152—153° (Found: C, 75·7; H, 10·9. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). The *mono*-3 : 5-*dinitrobenzoate*, readily formed in pyridine with one equivalent of reagent, had m. p. 214·0—215·5° (from acetone) (Found: C, 61·4; H, 6·7; N, 6·5. $C_{22}H_{28}O_7N_2$ requires C, 61·1; H, 6·5; N, 6·5%).

The $C_{15}H_{24}O_2$ *Tricyclic Ketone* (XII).—The glycol (16·5 g.) in glacial acetic acid (75 ml.) was treated with chromium trioxide (9·3 g.) in aqueous acetic acid, the temperature being kept below 25°. Next morning the mixture was diluted with water and extracted many times with ether, and the extracts were washed with carbonate solution. Evaporation left a thick oil that crystallised spontaneously. Recrystallisation from hexane and from ethanol–water gave 9 g. of pure 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$]dodecane-2 : 9-dione (XII), m. p. 50—51°, analysed as the *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 228—232·5° (decomp.) (Found: C, 54·4; H, 5·25; N, 18·8. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1; N, 18·85%). Acidification of the carbonate washings furnished a thick oil (1·54 g.) that solidified. Recrystallisation from ethyl

acetate gave prisms, m. p. 230—231·5°, of *5-carboxy-1 : 1 : 5-trimethyl-3-oxohexahydroindan-9-yl-acetic acid* (Found : C, 63·65; H, 7·8%; equiv., 139. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·9%; equiv., 141).

Clovane from the Tricyclic Diketone.—The diketone (9 g.) in diethylene glycol (100 ml.) was refluxed with potassium hydroxide (13 g.) and hydrazine hydrate (10 ml.; 85%) for 1·5 hr. Then, following Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487), the water was distilled off, and the mixture refluxed for 4 hr. The product was extracted in ether, washed, dried, and after removal of the ether, distilled from metallic sodium, yielding 6·02 g. (76·2%) of clovane, b. p. 115°/12 mm., $n_D^{25\cdot0}$ 1·4865, $[\alpha]_D^{26\cdot0}$ −5·3° (in $CHCl_3$; *c* 5·12) (Found : C, 87·45; H, 12·8%).

pseudo*Clovene.*—β-Caryophyllene alcohol (265 g.) was dehydrated as described by Henderson, McCrone, and Robertson (*loc. cit.*) to give a 95·5% yield of crude product. Distillation at 1·5 mm. gave 220 g., b. p. 85—93°; redistillation through the Stedman column yielded crude *pseudo*clovene, b. p. 112—124°/12·0 mm., $\alpha_D^{25\cdot0}$ +13·25° to +10·74°, and crude *iso*clovene, b. p. 125—127°, $\alpha_D^{25\cdot0}$ −0·83° to −46·46°. Refractionation of *pseudo*clovene gave, as the best fraction, b. p. 119·6°/12·0 mm., $n_D^{25\cdot0}$ 1·4928, $\alpha_D^{25\cdot0}$ +17·70°, although a fraction, b. p. 113·7°, $n_D^{25\cdot0}$ 1·4890, $\alpha_D^{25\cdot0}$ +13·40°, gave an infra-red spectrum identical with that of the higher-boiling specimen.

*Pseudo*Clovene readily absorbed bromine, with liberation of some hydrogen bromide, but the product gave off large volumes of hydrogen bromide at room temperature. With *N*-bromosuccinimide substitution readily occurred, but isolation of the product was accompanied by the loss of much hydrogen bromide.

Oxidation of *pseudo*clovene (similar to that of clovene) with ozone yielded the oily dibasic *pseudo*clovenic acid, purified as *dimethyl* pseudo*clovenate*, b. p. 112°/0·05 mm., $n_D^{25\cdot0}$ 1·4759 (Found : C, 68·8; H, 9·5. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%). *Dimethyl dibromo*pseudo*clovenate*, b. p. (bath temp.) 60°/10^{-3} mm. (Found : Br, 35·9. $C_{17}H_{26}O_4Br_2$ requires Br, 35·2%), was prepared from the acid (12·6 g.), phosphorus pentachloride (21·6 g.), and bromine (18·5 g.) that had been dried over phosphoric oxide; the mixture was warmed with an infra-red lamp, and after being kept overnight was treated with methanol.

Dehydration of β-Caryophyllene Alcohol with Sulphuric Acid.—The alcohol (15 g.) was dissolved in ether (50 ml.), and concentrated sulphuric acid (20 ml.) was added dropwise, the temperature reaching 50°. The mixture was then warmed on the water-bath for 1 hr. at 75°. The products were poured into water, neutralised with 20% sodium hydroxide solution, and extracted with ether. The product was an oil (10 g., 72·5%), which when fractionated from sodium through a Vigreux column gave as one fraction, b. p. 120—121°/13 mm., $n_D^{25\cdot0}$ 1·4865, $[\alpha]_D^{27\cdot5}$ −30·6° (in $CHCl_3$; *c* 3·53), a mixture (Found : C, 87·2; H, 12·6. Calc. for $C_{15}H_{26}$: C, 87·3; H, 12·7%) of saturated (mainly) and unsaturated material. Quantitative hydrogenation showed the mixture to contain 28·2% of unsaturated constituent.

Oxidation of the Dehydration Mixture.—The above mixture (6·1 g.) in glacial acetic acid (75 ml.) was treated with chromium trioxide (8·0 g.) in acetic acid (25 ml.) containing 2 ml. of water. After 2 hr. at 65—70°, the mixture was worked up to yield an acid (2·5 g.) and a neutral fraction (3·6 g.). The acid was esterified with diazomethane, furnishing the ester, b. p. 125—127°/1·0 mm., $n_D^{25\cdot0}$ 1·4725, of a keto-acid (Found : C, 70·2; H, 9·9. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·1%). The neutral fraction was proved to be β-caryophyllene alcohol by direct comparison with authentic material.

One of the authors (A. W. L.) gratefully acknowledges receipt of a grant-in-aid from the Hynson-Westcott and Dunning Fund.

THE JOHNS HOPKINS UNIVERSITY,
BALTIMORE 18, MARYLAND, U.S.A.

[*Received, December 18th*, 1953.]

Oxidation Studies. Part I. Metal-catalysed Persulphate Oxidation of Some Simple Phenols.

By R. G. R. Bacon, R. Grime, and D. J. Munro.

[Reprint Order No. 4905.]

The oxidation of phenol and *o*-, *m*-, and *p*-cresol by aqueous persulphate solutions is strongly catalysed by silver, ferrous, or ferric, but not by other ions examined. Oxidation by $S_2O_8^{2-}$–Fe^{3+} is much faster than by Fe^{3+} alone. Reaction is believed to proceed by mechanisms which involve $\cdot SO_4^-$ radicals and, in the case of silver catalysis, transient higher-valency ions, Ag^{2+} or Ag^{3+}.

Resinous polyphenols constitute almost the entire product from phenol and *o*- or *m*-cresol, but with *p*-cresol the following known crystalline products of oxidative coupling (~30% in all) were isolated: 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl, 2 : 2′ : 2″-trihydroxy-5 : 5′ : 5″-trimethyl-*m*-terphenyl, and a tetrahydrodimethyloxodibenzofuran. In the polyphenols the presence of 3—7 phenol units per molecule is indicated, and they contain, on average, about 0·2 atom of additional oxygen per phenol unit, probably introduced *via* nuclear hydroxylation, since small amounts of surviving mononuclear quinones were detected.

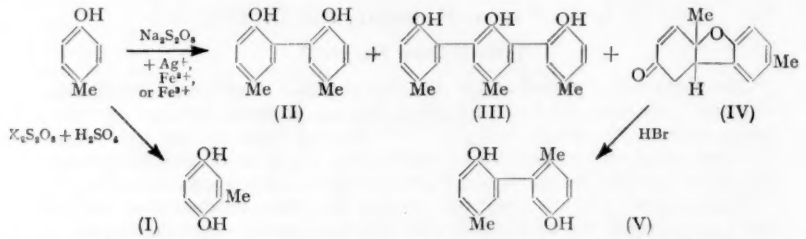
We recently summarised the results obtained by oxidising various kinds of aromatic compounds with aqueous persulphate solutions, particularly in the presence of metal salts as catalysts (Bacon, Bott, Doggart, Grime, and Munro, *Chem. and Ind.*, 1953, 897). The present communication describes the oxidation, by this method, of phenol and of *o*-, *m*-, and *p*-cresol.

We have found that the inclusion of silver ions, in particular, converts an aqueous persulphate solution into a potent and widely applicable oxidant for organic compounds. This catalytic activity of silver with persulphate, discovered by Marshall (*Proc. Roy. Soc. Edinburgh*, 1891, **18**, 63; 1900, **23**, 163; 1902, **24**, 88), has been applied to inorganic oxidations (*e.g.*, Yost *et al.*, *J. Amer. Chem. Soc.*, 1926, **48**, 152; 1931, **53**, 3349; 1937, **59**, 2129) and to some organic reactions. The latter include the oxidation of oxalic acid (Kempf, *Ber.*, 1905, **38**, 3963; King, *J. Amer. Chem. Soc.*, 1927, **49**, 2689; 1928, **50**, 2089; Allen, *ibid.*, 1951, **73**, 3589), of *p*-benzoquinone (Kempf, *Ber.*, 1906, **39**, 3715), of toluene and thymol (Austin, *J.*, 1911, **99**, 262), of acetone (Bekier and Kijowski, *Roczn. Chem.*, 1935, **15**, 136) and of glycols (Greenspan, *Diss. Abs.*, 1952, **12**, 132). We find, incidentally, that oxidation of acetone is not fast enough to prevent use of aqueous acetone, if desired, as a solvent for some catalysed oxidations (see Table 4).

Crystalline Products from Catalysed Oxidation of the Phenols.—Kumagai and Wolffenstein (*Ber.*, 1908, **41**, 297) reported that acidic aqueous potassium persulphate converts *p*-cresol, at 70—80°, into toluquinol (I), the reaction apparently involving migration of a methyl group (cf. Raper, *J.*, 1938, 125). We have confirmed this transformation (unreported experiments by R. Grime) but have found that resins (~95%) greatly predominate over crystalline products. Likewise, oxidation by aqueous sodium persulphate at 20—40° gives resins. At these temperatures reaction is slow (~0·2% per hr. at 40°; see Table 3) but addition of silver nitrate both catalyses the oxidation and provides a much cleaner, semi-crystalline product (Tables 3 and 4). With $S_2O_8^{2-}$ and Ag^+ in the ratio 10 : 1 the increase in rate of product-formation is of the order of 100-fold and it is still very large with much lower proportions of silver (*e.g.*, at 100 : 1). Of numerous other metal ions tested, only iron salts proved obvious catalysts; both the ferrous and the ferric form were effective and they were comparable in their activity with silver.

Three known, crystalline dehydro-derivatives of *p*-cresol were isolated from the products of catalysed oxidation. The mainly crystalline neutral fraction (20—40% in various runs) yielded a tetrahydrodimethyloxodibenzofuran (IV) and the mainly resinous alkali-soluble polycresol fraction yielded small amounts of 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (II) and 2 : 2′ : 2″-trihydroxy-5 : 5′ : 5″-trimethyl-*m*-terphenyl (III). The yields of these

three compounds are of the same order as in the best of previously recorded preparations (Table 1). The products were characterised by known derivatives and by the conversion of (II) and (III) into dibromides; ring-opening of (IV) yielded the diphenol (V).



Oxidation of phenol, *o*-cresol, and *m*-cresol was catalysed by silver ions as was that of *p*-cresol, but the precipitated products were entirely resinous and alkali-soluble. In the aqueous phase 1—2% of quinones were detected. As simple quinones readily undergo further oxidation, it is probable that larger amounts were initially formed; from 2 : 6-xylen-1-ol, which is blocked in both *ortho*-positions, the corresponding quinone is formed in substantial quantities under our conditions (Bacon and Munro, unpublished work).

TABLE 1.

Ref.	Agent	Dimeric phenol (II) (%)	Trimeric phenol (III) (%)	Ketone (IV) (%)
This paper	$Na_2S_2O_8 + Ag^+$, Fe^{2+}, or Fe^{3+}	7	7	15
a	Electrolytic oxidn.	11 (crude)	7 (crude)	—
b	Alkaline $K_3Fe(CN)_6$	1—2	2	13
c	H_2O_2 + peroxidase	2	7	13
d	$H_2O_2 + FeSO_4$	6	—	4
e	Solid $FeCl_3$	10—11	6—9	—
e	Aq. $FeCl_3$	5	—	1
f	Cl_2 or $SO_2Cl_2 + ZnCl_2$	12—16	3—8	—

[a] Fichter and Ackermann, *Helv. Chim. Acta*, 1919, **2**, 583, who describe (III) as an ether. [b] Pummerer, Melamed, and Puttfarcken, *Ber.*, 1922, **55**, 3116; Pummerer, Puttfarcken, and Schopflocker, *ibid.*, 1925, **58**, 1808. [c] Westerfeld and Lowe, *J. Biol. Chem.*, 1942, **145**, 463. [d] Cosgrove and Waters, *J.*, 1951, 1726, whose yields % are based on non-recovered cresol. [e] Bowden and Reece, *J.*, 1950, 2249. [f] *Idem*, *J.*, 1950, 1686.

Polymeric Products.—The polyphenols which constitute the main products are alkali-soluble resins, and appear to be mainly constituted of three or more phenol units per molecule. They are not the result solely of oxidative coupling, since representative samples (Table 2) contained additional oxygen.

TABLE 2.

	Average no. of phenol nuclei per mole	Average no. of O atoms per phenol nucleus
(*a*) Ether-insol. polymer from phenol.....	7	1·4
(*b*) Fraction from chromatography of polyphenol ...	4	1·25
(*c*) Fraction from chromatography of poly-*o*-cresol...	3·5	1·15
(*d*) Fraction from chromatography of poly-*m*-cresol	3	1·2

Notes: (i) A product such as (*b*) involves consumption of 1 mole of $Na_2S_2O_8$ per mole of phenol (as actually employed). (ii) In the Experimental section the oxygen is arbitrarily represented as hydroxylic.

Two observations demonstrate the stepwise formation of these complex oxidation products: in oxidation of *p*-cresol the consumption of persulphate continued after precipitation was complete (Table 3); and the crystalline diphenol (V) gradually resinified when stirred with the oxidant. The presence of small amounts of surviving mononuclear quinones in the aqueous phase suggests that extra oxygen may be acquired by introduction of nuclear hydroxyl groups, which then undergo further changes. Apart from this complication, there are two obvious causes of heterogeneity in the polymers. First, the linkages

between phenol units may be internuclear, as in (II) and (III), or may be through ether oxygen, as in (IV) (cf. Pummerer *et al.*, *loc. cit.*; *Chem. Ber.*, 1952, **85**, 535; 1953, **86**, 412), or may involve the methyl groups. Secondly, as in the case of phenol–formaldehyde resin formation, the number of structural isomers may vary from a maximum in phenol (which gave the most complex products) to a minimum in *p*-cresol (which gave the simplest products).

Reaction Mechanism.—The primary stage in catalysis of persulphate reactions by ferrous ions is generally accepted as being :

$$S_2O_8^{2-} + Fe^{2+} \longrightarrow SO_4^{2-} + \cdot SO_4^{-} + Fe^{3+}$$

(Merz and Waters, *Discuss. Faraday Soc.*, 1947, **2**, 179; *J.*, 1949, S 15; Kolthoff, Medalia, and Raaen, *J. Amer. Chem. Soc.*, 1951, **73**, 1733; Fordham and Williams, *ibid.*, p. 4855). Phenol oxidation may then involve dehydrogenation ($RH + \cdot SO_4^{-} \longrightarrow R\cdot + SO_4^{2-}$), followed by coupling of the resulting radicals (hydroxyaryl or aryloxy) as suggested in the similar case of oxidation by the H_2O_2–Fe^{2+} system (Cosgrove and Waters, *loc. cit.*).

By analogy, the primary steps in silver catalysis may be represented :

$$S_2O_8^{2-} + Ag^{+} \longrightarrow SO_4^{2-} + \cdot SO_4^{-} + Ag^{2+}$$
$$\cdot SO_4^{-} + Ag^{2+} \longrightarrow SO_4^{2-} + Ag^{3+}$$
$$(\text{or } S_2O_8^{2-} + Ag^{2+} \longrightarrow SO_4^{2-} + \cdot SO_4^{-} + Ag^{3+})$$

Transient bi- or ter-valent silver ions were postulated in $S_2O_8^{2-}$–Ag^{+} systems by Marshall, by Austin, and by Yost (*locc. cit.*) and there is evidence for their existence from other sources (Kleinberg, " Unfamiliar Oxidation States and Their Stabilisation," Univ. Kansas Press, Lawrence, U.S.A., 1950). The production of free radicals in the $S_2O_8^{2-}$–Ag^{+} system is supported by the fact that it behaves as a powerful redox catalyst for vinyl polymerisations (Bacon, *Trans. Faraday Soc.*, 1946, **42**, 140; Morgan, *ibid.*, p. 169). Although persulphate and silver salts react rapidly (giving a black hydrolysis product of the higher-valency salt if no oxidisable substance is present), the catalysed phenol oxidations proceed to completion without any special precautions as to the method of mixing the reagents. This suggests that one reaction occurring in the system is a direct oxidation of the phenol by the unstable higher-valency ions, Ag^{+} thereby being regenerated (cf. Yost, *loc. cit.*). In the case of iron, this direct oxidation is, of course, observable by employing the ferric salt alone (cf. Bowden and Reece, *loc. cit.*) and it may explain why, here too, mixing conditions are not critical, and why both ferrous and ferric ions are catalysts. It is noteworthy, however, that the iron-catalysed reaction is much faster (yield of product being about ten times as great) as in a comparable reaction in which a ferric salt alone is the oxidant.

Experimental

M. p.s are corrected. Some analyses are by Mr. J. Henry, Microchemical Laboratory, Queen's University, Belfast.

Materials and Procedure.—Sodium persulphate (cf. Table 4) was 97—99% pure. Redistilled laboratory-grade phenols were employed; some comparative experiments were done with *p*-cresol prepared from purified *p*-toluidine. Oxidations were conducted by mixing separate solutions of the phenol, persulphate, and catalyst, and gently stirring the mixture, at constant temperature, in air.

In catalysed oxidations, turbidity developed within a few minutes of mixing, and the product was eventually recovered quantitatively as a precipitate from a brown solution. When treated with ether, the dried product left some insoluble residue, usually small and contaminated with inorganic material. The ether-soluble product was separated, by 2N-sodium hydroxide, into a neutral fraction and an alkali-soluble polyphenol fraction.

Oxidation of p-*Cresol.*—(a) *Products of silver-catalysed oxidation.* The following is typical of preparations carried out on a 0·1—1·5 molar scale at room temperature. An aqueous solution (1 l.) containing pure synthetic *p*-cresol (10·8 g., 0·1 mole), sodium persulphate (0·1 mole), and silver nitrate (0·01 mole) was left for 24 hr. at 17°. The dry weight of the precipitate was 10·5 g., of which the ether-insoluble portion, an amorphous brown powder, was 0·22 g. Treatment of the ether-soluble product gave a pale yellow, crystalline, neutral fraction (2·8 g., 26%) and a

brown, resinous, alkali-soluble polycresol fraction (7·8 g., 72%). Ether-extraction of the aqueous filtrate from the oxidation products yielded only a trace of oily material.

After one crystallisation from methanol the neutral fraction yielded tetrahydrodimethyloxodibenzofuran (IV) as colourless leaflets (1·65 g., 15%), m. p. 123·5°, raised to 125—125·5° by sublimation at 0·1 mm.; m. p.s previously recorded (Table 1) vary from 122° to 128° (Found : C, 78·4; H, 6·5. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·5%). The oxime had m. p. 199—201° (decomp.) (Found : C, 73·1; H, 6·5; N, 5·9. Calc. for $C_{14}H_{15}O_2N$: C, 73·4; H, 6·5; N, 6·1%); Pummerer *et al.* (*loc. cit.*) give 203—204°, Westerfeld and Lowe (*loc. cit.*) give 198—200°, and Bowden and Reece (*loc. cit.*) give 195°. The semicarbazone had m. p. 259° (decomp.); Pummerer *et al.* give 249—250° (decomp.) and Westerfeld and Lowe give 255—256°

Some unchanged *p*-cresol (0·75 g., 7%) was removed from the alkali-soluble fraction by steam-distillation. The residual polycresols were distilled *in vacuo* to yield resinous fractions (*A*), b. p. 140—160°/1 mm. (1·48 g., 13% of the wt. of *p*-cresol), and (*B*), b. p. 220—280°/1 mm. (2·75 g., 25%). Fraction (*A*) crystallised from benzene, to give 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (II) (0·8 g., 7%) as colourless prisms, m. p. 153—154° (Found : C, 78·5; H, 6·3. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·5%), characterised as the diacetate, m. p. 87—88° (cf. Pummerer *et al.*, *loc. cit.*), and by treatment with bromine (2 molar equiv. per mole) in glacial acetic acid, (?3 : 3′-)*dibromo*-2 : 2′-*dihydroxy*-5 : 5′-*dimethyldiphenyl* being obtained in colourless needles, m. p. 141—142°, after recrystallisation from aqueous ethanol (Found : C, 45·6; H, 3·0; Br, 42·8. $C_{14}H_{12}O_2Br_2$ requires C, 45·2; H, 3·3; Br, 42·9%).

Fraction (*B*), crystallised from benzene, gave colourless 2 : 2′ : 2″-trihydroxy-5 : 5′ : 5″-trimethyl-*m*-terphenyl (III) (0·75 g., 7%), m. p. 194—196° (Found : C, 78·6; H, 6·45. Calc. for $C_{21}H_{20}O_3$: C, 78·7; H, 6·3%); Pummerer *et al.* (*loc. cit.*) give m. p. 194°, Westerfeld and Lowe (*loc. cit.*) give 196·5°, and Bowden and Reece (*loc. cit.*) give 197°. Treatment, at room temperature, with bromine (>2 mol.) in glacial acetic acid yielded a crude derivative (99%, calc. as dibromide), which, after two recrystallisations from ethanol, had m. p. 284—286° (decomp.). Analysis (except that the bromine value is a little high) indicated the expected dibromide, (? 3 : 3″-)*dibromo*-2 : 2′ : 2″-*trihydroxy*-5 : 5′ : 5″-*trimethyl*-m-*terphenyl* (Found : C, 52·9; H, 3·9; Br, 34·6. $C_{21}H_{18}O_3Br_2$ requires C, 52·7; H, 3·8; Br, 33·5%).

Alternatively, the crude polycresols were separated chromatographically on alumina (Peter Spence, Type H), with chloroform and ethanol, total recoveries being 60—90%. The first fraction was (unexpectedly) tetrahydrodimethyloxodibenzofuran (2% of the polycresol sample), m. p. and mixed m. p. 123·5—124·5° (semicarbazone, m. p. 261—262°), followed by resinous fractions (nearly 50% of the sample) and then by semi-crystalline fractions (about 40% of the sample). The semi-crystalline products were recrystallised to give, from successive fractions, the phenols (II) and (III) (about 5% each, on *p*-cresol).

(b) *Rates of catalysed and non-catalysed oxidations.* Precipitated reaction products (from 250 ml.; solutions left for varying times) were isolated on tared crucibles. The amount of persulphate which had decomposed was determined by titration of the acid present in the filtrates. Yields (Table 3) are expressed as % by wt. of *p*-cresol.

TABLE 3.

	p-Cresol, 0·1M $Na_2S_2O_8$, 0·1M $AgNO_3$, 0·01M 20°				*p*-Cresol, 0·1M $Na_2S_2O_8$, 0·1M $AgNO_3$, 0·01M 40°					*p*-Cresol, 0·1M $Na_2S_2O_8$, 0·1M 40°			
Time (hr.)	3	8	17	25	1·2	2·1	3·0	5·5	19	20	49	100	193
Persulphate consumed (%)	33	60	88	95	52	72	86	95	98	21	39	63	90
Total product (%)	52	100	100	100	76	98	99	99	100	7	9	13	33
Ether-insol. product (%)	0	0	3	2	0	1	2	3	2				
Neutral product (%)	18	40	42	40	29	40	41	38	41				
Polycresols (%)	34	60	55	58	47	57	56	58	57				

(c) *Catalysed oxidations at* 40°. See Table 4.

When a higher proportion of persulphate and a lower proportion of silver were used, at a higher concentration and at a higher temperature (0·125 mole of *p*-cresol, 0·25 mole of $Na_2S_2O_8$, 0·001 mole of $AgNO_3$, stirred in 100 ml. of water, at 60° for 2 hr.), 28% of the persulphate was converted into oxygen and the product (100% yield) afforded (i) ether-insoluble resin (16%), corresponding in analysis to $(C_7H_{7\cdot6}O_{5\cdot3})_n$, (ii) neutral fraction (41%) yielding pure ketone (15%), (iii) polycresol fraction (43%) yielding 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (3%) by distillation at 1 mm.

(d) *Trials of various metal-ions as oxidation catalysts.* Trials were carried out under standard conditions (Table 3), at 40° for 20 hr., purified reagents being used. Silver nitrate, ferrous sulphate, and ferric ammonium sulphate showed effects like those reported in Table 4. The following showed no catalytic effect, *i.e.*, a trace of tar was precipitated and the odour of *p*-cresol persisted: copper nitrate, potassium gold cyanide, zinc sulphate, mercurous nitrate, potassium aluminium sulphate, thallous nitrate, ceric ammonium nitrate, thorium nitrate, stannous or stannic sulphate, lead nitrate, vanadium sulphate (vanadium pentoxide dissolved in concentrated sulphuric acid), bismuth sulphate, chromium potassium sulphate, ammonium molybdate, sodium tungstate, uranyl nitrate, manganese sulphate, cobalt nitrate, and nickel sulphate.

TABLE 4.

1-l. scale; 0·1M-*p*-cresol, 0·1M-persulphate, 0·01M-catalyst; yields as % by wt. of *p*-cresol.

Expt.	Solvent	Per-sulphate	Catalyst	Total time of treat-ment (hr.)	Total product (%)	Ether-insol. product (%)	Neutral product: Total crude (%)	Neutral product: Pure ketone (%)	Poly-cresols (%)
1	H_2O	$Na_2S_2O_8$	None	24	10	—	—	—	—
2	,,	,,	$AgNO_3$	13	98	3	34	18	62
3	,,	$K_2S_2O_8$	,,	17	99	3	19	11	78
4	,,	$(NH_4)_2S_2O_8$	,,	19	100	3	19	13	79
5	Aq. acetone (1 : 1 v/v)	$Na_2S_2O_8$	,,	90	98	36	17	8	45
6	H_2O	,,	$FeSO_4$	40	98	1	23	9	77
7	,,	,,	$Fe_2(SO_4)_3$	24	96	—	16	8	79

(1) 90% of the cresol was recovered unchanged from the aqueous phase. The product, a resin (*M*, ~250) yielded a little oil and crystals, m. p. 147—150°, on sublimation at 120°/0·05 mm. (4) Gas evolution, 62 ml. at N.T.P., representing 5·5% persulphate decomposition (if oxygen) or 2·8% (if nitrogen). (5) Reaction was almost complete in ~10 hr. (compared with ~5 hr. in water). After 7 days at 20° (precipitation almost complete in ~60 hr.) the neutral fraction was similar, but the ether-insoluble fraction was only 3%. In absence of *p*-cresol, persulphate decomposition at 20° was ~95% in ~50 hr. in both water and 1 : 1 aqueous acetone, whilst at 40° 12 hr. were required in water and 5 hr. in 1 : 1 aqueous acetone. (6) Transient deep blue colour; the course of the reaction and appearance of the products were similar to those observed in silver-catalysis. (7) Ferric ammonium sulphate used. Reaction proceeded similarly to (6).

(e) *Comparison of ferric-catalysed persulphate oxidation with oxidation by ferric salt.* Comparative experiments were carried out for 4 hr. at 40° with aqueous solutions (900 ml.) containing (i) *p*-cresol (0·1 mole) and ferric ammonium sulphate (0·1 mole), and (ii) *p*-cresol (0·1 mole), sodium persulphate (0·05 mole, equivalent in oxidising power to 0·1 mole of ferric salt), and ferric ammonium sulphate (0·005 mole). The former yielded 1·0 g. (9%) of rather oily precipitate and the latter yielded 8.2 g. (76%) of precipitate of the usual type.

(f) *Catalysed persulphate oxidation of 2 : 5′-dihydroxy-2′ : 5-dimethyldiphenyl.* Tetrahydrodimethyloxodibenzofuran (IV) (10 g.), prepared as described under (a), was converted by hydrobromic acid into 2 : 5′-dihydroxy-2′ : 5-dimethyldiphenyl (V), obtained, after recrystallisation, as a white powder (5·6 g.), m. p. 161—161·5° (Pummerer *et al.*, *loc. cit.*, give 158°; Westerfeld and Lowe, *loc. cit.*, give m. p. 157·5—158·5°). This phenol (5·35 g., 0·025 mole) was stirred for 7 days at 40° in an aqueous solution (250 ml.) of sodium persulphate (0·025 mole) and silver nitrate (0·0025 mole). The filtered and dried product (5·72 g., 107% of the wt. of the phenol) yielded a resinous ether-insoluble fraction (1·87 g., 33%) of high ash-content. The ether-soluble product yielded a trace (0·03 g., 0·5%) of oily neutral material and a resinous alkali-soluble fraction (3·81 g., 67%), which was chromatographed (benzene and ether) on silica gel. The first fractions contained unchanged dihydroxydimethyldiphenyl (0·95 g., 18%), m. p. 159—161°, mixed m. p. 160—161·5°, but the later fractions were entirely resinous.

Oxidation of Phenol.—An aqueous solution (500 ml.) containing phenol (4·70 g., 0·05 mole), sodium persulphate (0·05 mole), and silver nitrate (0·005 mole) underwent rapid oxidation at 40°, but was left for 20 hr. The total crude tarry product (3·81 g., 81% of the wt. of phenol) was repeatedly triturated with ether, which left undissolved about 1·6 g. (34%) of dark resin, soluble in aqueous sodium hydroxide and in acetone, though not in benzene. Analysis corresponded approximately with polyphenols containing an average of 7 benzene nuclei and 10 (?) hydroxyl groups per mole [Found: C, 72·0; H, 4·6%; *M* (Rast), 670. Calc. for $C_{42}H_{20}(OH)_{10}$: C, 72·6; H, 4·4%; *M*, 694]. The ether-soluble products contained traces of tarry neutral material (0·2%) and unchanged phenol (1%) but were essentially alkali-soluble polyphenols (2·23 g.,

47%), which were chromatographed on alumina, benzene, ether, chloroform, and methanol being used. About half of the material could not thus be removed from the column. All the fractions were resinous. A typical sample corresponded approximately in analysis with polyphenols containing an average of 4 benzene nuclei and 4·5 (?) hydroxyl groups per mole [Found: Ash, 0·9, 2·2, 0; C, on ash-free basis, 75·9, 75·2, 75·6; H, on ash-free basis, 5·1, 5·0, 5·2%; *M* (Rast), 356, 385. Calc. for $C_{24}H_{13\cdot5}(OH)_{4\cdot5}$: C, 76·2; H, 4·8%; *M*, 381].

The red aqueous filtrate from the oxidation products possessed a strong odour of both phenol and *p*-benzoquinone. Ether-extraction yielded red needles (0·87 g., 18·5% of the wt. of phenol taken for oxidation), apparently a mixture of unchanged phenol with the red adduct of phenol and *p*-benzoquinone, but neither this product nor artificial mixtures of phenol and *p*-benzoquinone could be satisfactorily separated into pure components. The quinone content of the mixture was therefore determined by Willstätter and Majima's iodide method (*Ber.*, 1910, **43**, 1175). Artificial mixtures of phenol and *p*-benzoquinone gave results within 1% of the theoretical values (recommended time of shaking increased from 3 to 10 min.) and the reaction product was found to contain 7% of *p*-benzoquinone, corresponding with 1% conversion of the original phenol.

Oxidation of o-*Cresol.*—*o*-Cresol (0·05 mole) was oxidised similarly to phenol. Rapid darkening and deposition of particles of black, amorphous solid occurred. The reaction product (4·85 g., 90% of the wt. of *o*-cresol) contained 0·20 g. (4%) of an ether-insoluble fraction, which was readily soluble in 2N-sodium hydroxide and gave an ash-content of 14%. The ether-soluble product consisted of a small neutral fraction (4%), a trace of unchanged *o*-cresol, and the main alkali-soluble polycresol fraction (4·68 g., 87%). The last was separated by chromatographic treatment, as described for phenol products, into 25 resinous fractions (75% recovery from the column), two of which showed the following compositions: (*A*) Found: Ash, 0·3, 0·6; C, on ash-free basis, 77·4, 77·5; H, on ash-free basis, 6·2, 6·2%; *M* (Rast), 374, 385. (*B*) Found: ash, nil; C, 77·0, 76·8; H, 6·2, 6·2% [Calc. for polycresols with an average of 3 benzene nuclei and 3·5 (?) hydroxyl groups per mole, $C_{21}H_{16\cdot5}(OH)_{3\cdot5}$: C, 76·8; H, 6·1%; *M*, 328; for polycresols with an average of 4 benzene rings and 4·5 (?) hydroxyl groups per mole, $C_{28}H_{21\cdot5}(OH)_{4\cdot5}$: C, 77·4; H, 6·0%; *M*, 434].

The red-brown aqueous filtrate from the oxidation products yielded, on ether-extraction, a red mixture of crystals and phenolic oil (0·47 g., 9% of the wt. of *o*-cresol). Analysis of this by the method described under phenol indicated a quinone (? toluquinone) content of 20%, corresponding with 2% conversion of the original *o*-cresol.

Oxidation of m-*Cresol.*—*m*-Cresol (0·05 mole) was oxidised similarly to phenol. Formation of precipitate, consisting of red-brown powder and tar, was rapid. The crude product (5·28 g., 98% of the wt. of cresol) yielded a small ether-insoluble fraction (1%) as a red-brown powder with a high ash-content. The ether-soluble product consisted of alkali-soluble polycresols (5·0 g., 93%), a little unchanged cresol (3%), and neutral material (0·7%). The polycresols, subjected to chromatography, as described for the phenol products, yielded 14 resinous fractions (86% recovery from the column). A sample, representative of the earlier fractions, corresponded approximately in analysis with an average of 3 benzene nuclei and 3·5 (?) hydroxyl groups per mole [Found: C, 76·8, 76·9; H, 6·5, 6·4%; *M* (Rast), 349, 308. Calc. for $C_{21}H_{16\cdot5}(OH)_{3\cdot5}$: C, 76·8; H, 6·1%; *M*, 328].

Ether-extraction of the aqueous filtrate from the oxidation products yielded some phenolic brown oil (0·08 g., 1·5% of the wt. of cresol). Analysis as described under phenol, indicated a quinone (? toluquinone) content of 19%, corresponding with only 0·3% conversion of the cresol.

QUEEN'S UNIVERSITY, BELFAST.

[*Received, December 19th*, 1953.]

The Organic Chemistry of Phosphorus. Part II. The Action of Triphenyl Phosphite Dihalides on Alcohols: Two Further New Methods for the Preparation of Alkyl Halides.*

By D. G. Coe, S. R. Landauer, and H. N. Rydon.

[Reprint Order No. 5117.]

Alkyl halides may be prepared conveniently and in good yield from triphenyl phosphite, an alcohol, and a halogen, either by adding the halogen to a mixture of the alcohol and the phosphite:

$$(PhO)_3P + ROH + Hal_2 \longrightarrow RHal + Hal{\cdot}PO(OPh)_2 + PhOH$$

or by first preparing the triphenyl phosphite dihalide and then treating this with the alcohol:

$$(PhO)_3PHal_2 + ROH \longrightarrow RHal + Hal{\cdot}PO(OPh)_2 + PhOH$$

The results obtained with mixed halogens are described and discussed and the mechanisms of the various reactions are considered briefly.

In Part I * several new methods for the preparation of alkyl halides, based on the overall reaction,

$$(PhO)_3P + ROH + XHal \longrightarrow RHal + X{\cdot}PO(OPh)_2 + PhOH$$

where X = alkyl, H, NH_4, Na, or Li, were described. In the present paper we describe the extension of this work to the case where X = halogen. As in the previous case, where XHal is an alkyl halide, so also in the present case where XHal is a halogen, the reaction can be carried out either by direct reaction between the three components or by first forming the addition compound of the halogen and the phosphite and treating this with the alcohol; both methods are of preparative value.

Triaryl phosphite dihalides, $(ArO)_3PHal_2$, (triaryloxyhalogenophosphonium halides if electrovalent, or triaryl dihalogenophosphoranetrioates if covalent) have previously been prepared, usually as uncrystallisable oils, by the action of halogen on triaryl phosphites (Noack, *Annalen*, 1883, **218**, 85; Anschütz and Emery, *ibid.*, 1889, **253**, 105; Autenrieth and Geyer, *Ber.*, 1908, **41**, 146; Anschütz, Boedeker, Broeker, and Wenger, *Annalen*, 1927, **454**, 71; Anschütz, Kraft, and Schmidt, *ibid.*, 1939, **542**, 14) and by the action of phosphorus pentahalides on three equivalents of a phenol (Autenrieth and Geyer, *loc. cit.*; Anschütz, Kraft, and Schmidt, *loc. cit.*). We have used the former method and have so obtained triphenyl phosphite dichloride, dibromide, di-iodide, bromo-chloride, bromo-iodide, and chloro-iodide as crystalline solids; the dichloride was obtained, analytically pure, as colourless prisms, m. p. 80—81°, by crystallisation from acetone–ether under strictly anhydrous conditions; work at present in progress on the purification of the other dihalides will be reported later.

Triphenyl phosphite dihalides react very readily with alcohols to form alkyl halides, thus:

$$(PhO)_3PHal_2 + ROH \longrightarrow RHal + Hal{\cdot}PO(OPh)_2 + PhOH$$

That the reaction takes this course, rather than the alternative:

$$(PhO)_3PHal_2 + ROH \longrightarrow RHal + (PhO)_3PO + HHal$$

as suggested by Milobendski and Kolitowska (*Roczn. Chem.*, 1926, **6**, 67), who obtained menthyl chloride by the action of triphenyl phosphite dichloride probably contaminated with phosphorus pentachloride on menthol, is shown by the presence of phenol in the reaction products and the absence of hydrogen halide and by the formation of diphenyl *N*-phenylphosphoramidate, $(PhO)_2PO{\cdot}NHPh$, by treatment of the reaction product with aniline. The experimental procedure is simple and convenient; the halogen is passed into, or added gradually to, one equivalent of triphenyl phosphite, with cooling and stirring;

* Part I, *J.*, 1953, 2224.

the crude dihalide so formed is treated dropwise, cooling if necessary, with one equivalent of the alcohol and the resulting alkyl halide is then isolated, usually by direct distillation. The reaction residue yields triphenyl phosphate when heated or on treatment with bases :

$$PhOH + Hal{\cdot}PO(OPh)_2 \longrightarrow HHal + (PhO)_3PO$$

The yields of seven representative alkyl halides varied from 60% to 98%. The reaction proceeds quite satisfactorily with unsaturated alcohols; substantial inversion of configuration occurs with octan-2-ol, but cholesterol yields the uninverted cholesteryl halide (cf. Part I, *loc. cit.*).

An even simpler method involves the direct reaction of the three components :

$$(PhO)_3P + ROH + Hal_2 \longrightarrow RHal + Hal{\cdot}PO(OPh)_2 + PhOH$$

the evidence for this reaction course being similar to that advanced above for the two-component reaction. The experimental procedure is extremely simple and rapid; one equivalent of the halogen is passed into, or added gradually to, a stirred mixture at 0° of one equivalent of the alcohol and one equivalent of triphenyl phosphite; after the reaction mixture has been kept at room temperature for some time, the alkyl halide is isolated by direct distillation or other convenient means. Yields in ten representative cases varied from 62% to 92%, the average being 72%; for obvious reasons this method is not very suitable for the preparation of unsaturated alkyl halides, for which the two-component procedure is quite satisfactory; like the two-component procedure, the method gave very unsatisfactory results with *cyclo*hexanol. This method is the simplest and most convenient of all those using triphenyl phosphite described in this paper and in Part I; in view of the ease and speed with which it may be carried out, the low temperature at which it proceeds, and the commercial availability, at low cost, of triphenyl phosphite, the method may well be preferred to the older and more conventional methods for the preparation of saturated alkyl halides of all kinds; for unsaturated halides, the method using the pre-formed triphenyl phosphite dihalides is the method of choice. If two equivalents of alcohol are used, the initial reaction leads to the formation of a mixed alkyl phenyl phosphorohalidate; such compounds may decompose on being heated to yield a second equivalent of alkyl halide (Balarew, *Z. anorg. Chem.*, 1917, **99**, 187; **101**, 225) :

$$Hal{\cdot}PO(OR)(OPh) \longrightarrow RHal + PhO{\cdot}PO_2$$

The decomposition temperature of the phosphorochloridates (cf. Gerrard, *J.*, 1940, 1464) and phosphorobromidates is too high for this reaction to be of practical value but the phosphoroiodidates decompose at lower temperatures and a considerable economy in iodine can be achieved in the preparation of *n*-butyl iodide, and presumably of other alkyl iodides, by using two equivalents of the alcohol.

Both of the preparative reactions just discussed can be accommodated within the obvious modification of the general scheme advanced in Part I (*loc. cit.*, p. 2227) for the similar reactions of methyl iodide, which it does not seem necessary to reproduce.

Considerable interest attaches to the course of both reactions when a mixed halogen (halogen halide) is used. The average results of numerous experiments carried out using pre-formed dihalides are given in Table 1. Qualitatively similar results were obtained in

TABLE 1. *Molar ratios of alkyl halides from butyl alcohols and triphenyl phosphite dihalides.*

	$(PhO)_3PClBr$ RBr : RCl	$(PhO)_3PClI$ RI : RCl	$(PhO)_3PBrI$ RI : RBr
n-Butyl alcohol	92 : 8	77 : 23	32 : 68
sec.-Butyl alcohol	100 : 0	75 : 25	21 : 79
tert.-Butyl alcohol	94 : 6	47 : 53	21 : 79

experiments in which iodine chloride was added to mixtures of the three butyl alcohols and triphenyl phosphite, and also in experiments in which *n*-butyl alcohol was treated with some diphenyl trihalogenophosphoranedioates and phenyl tetrahalogenophosphoranoates; the results of the latter experiments were :

	$(PhO)_2PClBr_2$	$(PhO)_2PCl_2Br$	$PhO{\cdot}PClBr_3$	$PhO{\cdot}PCl_2Br_2$	$PhO{\cdot}PCl_3Br$
Molar ratio, Bu^nBr : Bu^nCl ...	100 : 0	90 : 10	100 : 0	100 : 0	75 : 25

Experiments were also carried out with optically active octan-2-ol, with results summarised in Table 2.

TABLE 2. *Experiments with octan-2-ol.*

Dihalide	Products		
	Halide	Yield (%)	Inversion (%) *
$(PhO)_2PCl_2$	$C_8H_{17}Cl$	59	90
$(PhO)_2PI_2$	$C_8H_{17}I$	69	23
$(PhO)_2PClBr$	$C_8H_{17}Br$	73	56
	$C_8H_{17}Cl$	17	32
$(PhO)_2PClI$	$C_8H_{17}I$	47	65
	$C_8H_{17}Cl$	1	72
$(PhO)_2PBrI$	$C_8H_{17}I$	14	45
	$C_8H_{17}Br$	39	74

* Calc. from the specific rotations given by Brauns (*Rec. Trav. chim.*, 1946, **65**, 799); 100% indicates complete inversion, 0% complete racemisation.

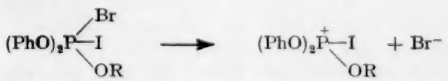
These results, except those relating to the action of triphenyl phosphite chloro-iodide on *tert.*-butyl alcohol, reveal a marked tendency for the formation of alkyl iodides and bromides in preference to chlorides, whereas alkyl bromides are formed in preference to iodides.

It will be convenient to consider first the results with the chloro-iodide and chloro-bromide. The observed high degree of optical inversion in the reactions with octan-2-ol (cf. the results of Gerrard and Green, *J.*, 1951, 2550, on the Arbusov reaction with tri-2-octyl phosphite) suggests attack on the ester-exchanged intermediate by halide ion (cf. Part I), thus:

It follows that, in the compounds under immediate consideration, it is the halogen other than chlorine which ionises, *e.g.*:

This at first sight appears anomalous, since the more electronegative halogen might have been expected to ionise preferentially, but the case is analogous to the well-known one of the reactivity of the alkyl halides and, like this, finds its explanation in the government of the ionisation by bond strength rather than electronegativity; the P–Cl bond (heat of formation, 77 kcal./mole) is much stronger than the P–Br and the P–I bond (heats of formation, 63·5 and 49·5 kcal./mole, respectively) and it is not unreasonable that the P–Cl linkage should be considerably more reluctant to ionise than the other two.

The results with the bromo-iodide are less easily explained, since here it is apparently the strongest link which ionises, thus:



In all such cases of competition for ionisation from a central phosphorus (or other) atom, each halogen will, by virtue of its electron-attracting capacity, reduce the tendency of the other to ionise; our results suggest that the effect of the bromine atom on the ionisation tendency of the iodine is so much greater than the similar effect of the iodine on the bromine as to result in preferential ionisation of the P–Br linkage, in spite of its greater strength; work is in hand with the object of obtaining experimental evidence on this point. The possibility that the reaction might lead initially to alkyl iodide and phosphoro-bromidate, which then undergo halogen exchange, has been excluded by direct experiment. The stereochemical similarity in the reactions of all three mixed dihalides with octan-2-ol at least lends no support to the suggestion that there may be some mechanistic singularity in the reaction with the bromo-iodide. There remains the possibility of some structural

difference between the chlorine-containing dihalides and the others (cf. phosphorus pentachloride and phosphorus pentabromide); this, too, we intend to investigate.

Experiments were also carried out on the action of bromine, iodine, iodine chloride, and iodine bromide on tri-*n*-butyl phosphite; the results (p. 2288) are difficult to interpret, since appreciably more than one mole of alkyl halide is formed, the second mole arising from decomposition of the dibutyl phosphorohalidate formed in the first stage of the reaction.

Experimental

(Rotations were determined without solvent in 1-dm. tubes.)

Preparation of Triphenyl Phosphite Dihalides.—These compounds are readily prepared by the direct action of halogens or mixed halogens on triphenyl phosphite with the rigorous exclusion of moisture. In the case of chlorine, the dried gas was passed into the phosphite, with cooling and stirring, until the theoretical amount had been taken up; with bromine and iodine chloride, the required amount of the halogen was added dropwise to the cooled and stirred phosphite; in the case of bromine chloride, the phosphite was slowly added to the halogen cooled to −40°; the di-iodide and bromo-iodide were prepared by adding the theoretical amount of powdered halogen to triphenyl phosphite and stirring the mixture overnight at room temperature. Although all the dihalides were obtained as crystalline solids, only the dichloride was further purified; the crude dihalides are quite suitable for reaction with alcohols.

Triphenyl phosphite dichloride. The crude dichloride (0·1 mole), prepared in liquid form by passing chlorine into triphenyl phosphite with slight cooling, was stirred vigorously with light petroleum (b. p. 60—80°; 100 ml.) and then with ether, whereupon it solidified to glistening colourless prisms, which were washed with ether by decantation. For recrystallisation, the compound, as a thick slurry in dry ether, was dissolved in the minimum amount of cold, dry acetone and then precipitated, as fine colourless prisms, by the addition of dry ether (½ vol.) with vigorous stirring. After decantation of the solvent and washing of the crystals with ether, the process was repeated until the m. p. was constant; the *dichloride* (*chlorotriphenoxyphosphonium chloride* or *triphenyl dichlorophosphoranetrioate*) has m. p. 80—81° (Found: Cl, 18·0. $C_{18}H_{15}O_3PCl_2$ requires Cl, 18·6%).

Preparation of Alkyl Halides from Triphenyl Phosphite Dihalides.—(a) n-*Butyl chloride.* *n*-Butyl alcohol (11 g.) was added dropwise to crude triphenyl phosphite dichloride (from triphenyl phosphite, 50 g.) at room temperature; the reaction was completed by gentle warming and the product distilled under reduced pressure into traps cooled to −80°. Distillation, washing of the fraction of b. p. 78—79° with water, drying, and redistillation afforded *n*-butyl chloride (10·5 g., 76%), b. p. 78—79°, n_D^{21} 1·4015.

(b) cyclo*Hexyl chloride.* *cyclo*Hexanol (15 g.) was added slowly to the dichloride from triphenyl phosphite (51 g.), and the mixture kept overnight at room temperature. Two distillations gave *cyclo*hexyl chloride (6·1 g., 34%), b. p. 90—95°/65 mm., n_D^{22} 1·4612.

(c) *Allyl bromide.* Allyl alcohol (5·8 g.) was added slowly to the dibromide from triphenyl phosphite (34 g.), with cooling. After the vigorous reaction had abated, the mixture was distilled under reduced pressure into traps cooled to −80°. Redistillation of the washed condensate gave allyl bromide (9 g., 75%), b. p. 70—72°, n_D^{26} 1·4650. Dimethylaniline (6 g.) was added cautiously to the residue from the original distillation; the product was kept at room temperature for an hour and then treated with ether (250 ml.). After being washed with 10% methanol, 2N-sodium hydroxide, and water, the dried solution was evaporated and the solid residue of crude triphenyl phosphate (32 g., 98%; m. p. 39°) recrystallised from light petroleum (b. p. 40—60°), yielding the pure phosphate as long needles, m. p. and mixed m. p. 47°.

(d) *Cholesteryl bromide.* Cholesterol (2 g.) was added to the dibromide from triphenyl phosphite (6 g.) and the mixture warmed at 60—70° for 15 min. The product was diluted with acetone (50 ml.) and cooled; cholesteryl bromide (1·4 g.; m. p. 86—90°) separated in platelets and a further crop (0·8 g.; m. p. 89—90°) was obtained by diluting the filtrate with water. Two recrystallisations from ethyl acetate gave the pure bromide, m. p. 97—98° (Found: Br, 18·05. Calc. for $C_{27}H_{45}Br$: Br, 17·8%).

(e) n-*Butyl iodide.* *n*-Butyl alcohol (7·4 g.) was slowly added to the di-iodide from triphenyl phosphite (34 g.). After the vigorous reaction had abated, the product was distilled under reduced pressure into traps at −80°; washing and redistillation gave *n*-butyl iodide (16 g.,

87%), b. p. 129—131°, n_D^{23} 1·4980. The residue from the initial distillation was heated at 250° for 3 hr. and then dissolved in ether (100 ml.) and washed with 10% methanol, 2N-sodium hydroxide, and water. Evaporation of the dried extract gave triphenyl phosphate (25 g., 70%), m. p. 37° raised to 46° by recrystallisation from light petroleum (b. p. 40—60°).

(f) tert.-*Butyl iodide*. *tert.*-Butyl alcohol (8 g.) was added dropwise to the di-iodide from triphenyl phosphite (34 g.), and the mixture was kept at room temperature for 30 min. Two distillations gave *tert.*-butyl iodide (15 g., 83%), b. p. 95°, n_D^{20} 1·4890.

Preparation of Alkyl Halides from Triphenyl Phosphite, Halogens, and Alcohols.—The appropriate halogen was added dropwise to, or passed into, a stirred mixture of the alcohol and triphenyl phosphite at 0°. After being kept at room temperature for some time, the crude alkyl halide was distilled from the reaction mixture under reduced pressure, washed, dried, and re-distilled.

Preparative experiments, on the 0·1-molar scale, are summarised in Table 3.

TABLE 3. *Alkyl halides from triphenyl phosphite, halogens, and alcohols.*

Reactants (and molar ratio)	Reaction time (hr.)	Product: Yield (%; based on alcohol)	Product: B. p.	Product: n_D^{20}
Bu^nOH, Cl_2, $(PhO)_3P$ (2 : 1 : 1)	2	Bu^nCl, 49	—	1·4050
Bu^nOH, Br_2, $(PhO)_3P$ (1 : 1 : 1) [1]	1	Bu^nBr, 80	100—101°	1·4400
Bu^nOH, Br_2, $(PhO)_3P$ (2 : 1 : 1)	3	Bu^nBr, 58	—	1·4403
Bu^nOH, I_2, $(PhO)_3P$ (2 : 1 : 1) [2]	2	Bu^nI, 75	123—126°	1·5001
Bu^nOH, ICl, $(PhO)_3P$ (1 : 1 : 1)	1	Bu^nCl, 23; Bu^nI, 65	—	1·4749
Bu^sOH, ICl, $(PhO)_3P$ (1 : 1 : 1)	1	Bu^sCl, 14; Bu^sI, 61	—	1·4762
Bu^tOH, Cl_2, $(PhO)_3P$ (1 : 1 : 1)	1	Bu^tCl, 62	54°	1·4018
Bu^tOH, Br_2, $(PhO)_3P$ (1 : 1 : 1) [3]	1	Bu^tBr, 76	70°	1·4283
Bu^tOH, Br_2, $(C_7H_8O)_3P$ (1 : 1 : 1) [4] ...	1	Bu^tBr, 85	72°	1·4300 (n_D^{18})
Bu^tOH, ICl, $(PhO)_3P$ (1 : 1 : 1)	1	Bu^tCl, 39; Bu^tI, 46	—	1·4420
$HO\cdot[CH_2]_3\cdot OH$, Cl_2, $(PhO)_3P$ (1 : 2 : 1)	1	$Cl\cdot[CH_2]_3\cdot Cl$, 63	70—73°/50 mm.	1·4470
$HO\cdot[CH_2]_3\cdot OH$, Br_2, $(PhO)_3P$ (1 : 2 : 1) [5]	1	$Br\cdot[CH_2]_3\cdot Br$, 92	90°/80 mm.	1·5250
Et lactate, Cl_2, $(PhO)_3P$ (1 : 1 : 1)	1	Et α-chloropropionate, 79	70°/60 mm.	1·4209 (n_D^{14})
Et lactate, Br_2, $(PhO)_3P$ (1 : 1 : 1) ...	1	Et α-bromopropionate, 82	70°/30 mm.	1·4460
$Ph\cdot CH_2\cdot CH_2\cdot OH$, Cl_2, $(PhO)_3P$ (1 : 1 : 1)	1	$Ph\cdot CH_2\cdot CH_2Cl$, 78	105°/20 mm.	1·5273
$Ph\cdot CH_2\cdot CH_2\cdot OH$, Br_2, $(PhO)_3P$ (1 : 1 : 1)	1	$Ph\cdot CH_2\cdot CH_2Br$, 82	120°/10 mm.	1·5570

[1] Distillation of the residue gave a 53% yield of triphenyl phosphate. [2] The alcohol and phosphite were heated for 90 min. at 100° before addition of the iodine. [3] The residue was dissolved in ether (50 ml.), shaken with 100-ml. portions of 10% sodium hydroxide, 10% methanol, and water, dried, and evaporated; crystallisation of the residue from light petroleum (b. p. 40—60°) gave triphenyl phosphate (15·5 g., 48%), m. p. 47°. [4] Tri-*p*-tolyl phosphite (Michaelis and Kähne, *Ber.*, 1898, **31**, 1048) was used in this experiment. [5] Distillation of the residue gave a 45% yield of triphenyl phosphate.

Formation of Diphenyl Phosphorohalidates.—Bromine (16·2 g., 0·1 mole) was added dropwise, with stirring, to an ice-cooled mixture of triphenyl phosphite (34 g., 0·11 mole) and *tert.*-butyl alcohol (7·4 g., 0·1 mole). The mixture was kept at room temperature for 1 hr. and aniline (24 g., 0·25 mole) was then added rapidly with vigorous stirring; after 48 hr., the mixture was heated at 100° for 30 min. and then steam-distilled to remove phenol and excess of aniline. The organic part of the residue solidified (m. p. 115—120°) and was identified as diphenyl *N*-phenylphosphoramidate (25·5 g., 70%) by crystallisation from ethanol (m. p. 130—131°; lit., m. p. 129—130°) (Found: N, 4·45. Calc. for $C_{18}H_{16}O_3NP$: N, 4·3%). The same compound was obtained similarly from the products of the action of iodine chloride on a mixture of triphenyl phosphite and *n*-butyl alcohol and of the action of triphenyl phosphite bromoiodide on *tert.*-butyl alcohol.

Action of Triphenyl Phosphite Dihalides on Butyl Alcohols.—The dihalide (0·2 mole), prepared in the usual manner, was kept for the time specified in Table 4, and the alcohol (0·2 mole) then added slowly, stirring being recommenced as soon as the mixture was sufficiently fluid. After completion of the addition, the mixture was set aside at room temperature for an hour and then distilled under reduced pressure into traps cooled to −80°, distillation being stopped when phenol began to distil over. The distillate was twice washed with 2N-sodium hydroxide and with water and finally dried (Na_2SO_4); the composition of the product was estimated from the refractive index and the refractive indices of the pure components determined at the same time. The results are summarised in Table 4.

Action of Diphenyl Trihalogenophosphoranedioates and Phenyl Tetrahalogenophosphoranoates on n-*Butyl Alcohol.*—(a) *Diphenyl dibromochlorophosphoranedioate.* Bromine (32 g., 0·2 mole)

was added dropwise, with cooling and stirring, to diphenyl phosphorochloridite (50·5 g.,) 0·2 mole) (b. p. 144—158°/2 mm.; n_D^{24} 1·5774; Noack, *Annalen*, 1883, **218**, 85); after the addition compound had solidified it was kept at room temperature for an hour. *n*-Butyl alcohol (15 g., 0·2 mole) was then added, with cooling, stirring being recommenced as soon as possible. Isolation of the product in the usual manner gave *n*-butyl bromide (24 g., 87%), n_4^{20} 1·4400, essentially free from the chloride.

TABLE 4. *Action of triphenyl phosphite dihalides on butyl alcohols.*

Reactants: Alcohol, ROH	Reactants: Dihalide	Period of keeping of dihalide before reaction (hr.)	Products (yield, %): RCl	RBr	RI	Molar ratio of products	Mean molar ratio of products
Bu^{n}OH	$(PhO)_2PClBr$	0·5	8	86	—	9 : 91	
,,	,,	1	11	87	—	11 : 89	8 : 92
,,	,,	18	0	94	—	0 : 100	
,,	,,	*	12	88	—	12 : 88	
,,	$(PhO)_2PClI$	0·5	21	—	58	27 : 73	
,,	,,	1	19	—	74	20 : 80	
,,	,,	1	21	—	74	22 : 78	
,,	,,	18	17	—	70	20 : 80	23 : 77
,,	,,	18 (100°)	18	—	67	21 : 79	
,,	,,	19	24	—	59	29 : 71	
,,	,,	120	19	—	72	21 : 79	
,,	$(PhO)_2PBrI$	0·5	—	62	35	64 : 36	
,,	,,	1	—	54	28	66 : 34	
,,	,,	1	—	64	30	68 : 32	
,,	,,	2	—	65	35	65 : 35	68 : 32
,,	,,	18	—	60	25	71 : 29	
,,	,,	18	—	65	23	74 : 26	
,,	,,	40	—	64	27	70 : 30	
Bu^{s}OH	$(PhO)_2PClBr$	1·5	0	87	—	0 : 100	0 : 100
,,	,,	18	0	92	—	0 : 100	
,,	$(PhO)_2PClI$	0·5	22	—	54	29 : 71	
,,	,,	1	12	—	68	15 : 85	25 : 75
,,	,,	18	23	—	53	30 : 70	
,,	$(PhO)_2PBrI$	1	—	60	26	70 : 30	
,,	,,	1	—	76	20	79 : 21	79 : 21
,,	,,	18	—	68	20	77 : 23	
,,	,,	60	—	86	11	89 : 11	
Bu^{t}OH	$(PhO)_2PClBr$	1	0	91	—	0 : 100	7 : 93
,,	,,	60	12	79	—	13 : 87	
,,	$(PhO)_2PClI$	1	46	—	39	54 : 46	
,,	,,	1	37	—	44	46 : 54	
,,	,,	1	38	—	31	55 : 45	53 : 47
,,	,,	18	51	—	47	52 : 48	
,,	,,	24	46	—	34	57 : 43	
,,	$(PhO)_2PBrI$	0·5	—	76	16	83 : 17	
,,	,,	1	—	68	19	78 : 22	
,,	,,	18	—	67	22	75 : 25	79 : 21
,,	,,	18	—	75	15	83 : 17	
,,	,,	21	—	61	17	78 : 22	

* Chlorine (0·05 mole) was passed into triphenyl phosphite (0·1 mole); bromine (0·05 mole) was then added and the mixture heated at 100° for 20 min. After cooling, the reaction was carried out as usual.

(b) *Diphenyl bromodichlorophosphoranedioate.* Diphenyl phosphorochloridite (50·5 g., 0·2 mole) was added very cautiously to bromine chloride (23 g., 0·2 mole) at −70° and the resulting addition compound treated with *n*-butyl alcohol (15 g., 0·2 mole). The product (22·2 g.; n_D^{20} 1·4354) was a mixture of *n*-butyl chloride (1·9 g., 10%) and *n*-butyl bromide (20·3 g., 74%).

(c) *Phenyl bromotrichlorophosphoranoate.* Phenyl phosphorodichloridite (39 g., 0·2 mole; b. p. 57—58°/2 mm., n_D^{25} 1·5578; Noack, *loc. cit.*) was added cautiously to bromine chloride (23 g., 0·2 mole), and the resulting addition compound treated with *n*-butyl alcohol (15 g., 0·2 mole). The product (15 g.; n_D^{20} 1·4315) was a mixture of *n*-butyl chloride (13% yield) and *n*-butyl bromide (46% yield).

(d) *Phenyl dibromodichlorophosphoranoate.* Bromine (32 g., 0·2 mole) was added to phenyl phosphorodichloridite (39 g., 0·2 mole), and the resulting addition compound treated with *n*-butyl alcohol (15 g., 0·2 mole); much hydrogen chloride was evolved and an additional amount of *n*-butyl alcohol (2 g.) had to be added to complete the dissolution of the addition

compound. The halide formed, isolated in the usual manner, was essentially pure *n*-butyl bromide (25 g., 91%), n_D^{20} 1·4403. The residue from the initial distillation was treated with an excess of aniline; steam-distillation left a solid (35 g.), which, on repeated crystallisation from ethanol and chromatography on alumina in benzene–chloroform (1 : 1), yielded phenyl *NN'*-diphenylphosphorodiamidate, m. p. 177—178° (Audrieth and Toy, *J. Amer. Chem. Soc.*, 1942, **64**, 1337, give m. p. 179—180°) (Found: C, 67·7; H, 5·4; N, 8·2. Calc. for $C_{18}H_{17}O_2N_2P$: C, 66·7; H, 5·25; N, 8·6%).

(e) *Phenyl tribromochlorophosphoranoate.* Phenyl phosphorodibromidite (57 g., 0·2 mole; b. p. 125—130°/11 mm.; Strecker and Grossmann, *Ber.*, 1916, **49**, 63) was added cautiously to bromine chloride (23 g., 0·2 mole) at −70° and the resulting addition compound treated with *n*-butyl alcohol (15 g., 0·2 mole). Hydrogen halide was evolved and it was necessary to add more *n*-butyl alcohol (1·5 g.) to complete the dissolution of the addition compound. Working up in the usual manner gave essentially pure *n*-butyl bromide (28 g., 100%), n_D^{20} 1·4402.

Action of Triphenyl Phosphite Dihalides on Octan-2-ol.—Octan-2-ol was resolved by the method of Pickard and Kenyon (*J.*, 1907, **91**, 2058); the triphenyl phosphite dihalides were prepared by slowly adding the appropriate halogen to cooled, stirred triphenyl phosphite and keeping the mixture for 24 hr. The dihalide was then treated, with cooling and stirring, with octan-2-ol, and the mixture was set aside for 30 min. and then distilled under reduced pressure into traps cooled to −70°. The distillate was dissolved in ether, washed with sodium hydroxide and water, dried (Na_2SO_4), and distilled.

The composition of each fraction was determined from its refractive index. In every case one fraction consisted of a pure halide and it was thus possible, by using the observed rotation of this fraction, to calculate the rotation of the other halide present in the other fractions from the observed rotations; the rotations given for this second halide are the means of the values calculated in this way.

Triphenyl phosphite dichloride. (+)-Octan-2-ol (13 g.; $[\alpha]_D^{21}$ +8·72°) gave (−)-2-chloro-octane (8·7 g., 59%), b. p. 59°/13 mm., n_D^{20} 1·4265, $[\alpha]_D^{21}$ −28·67°.

Triphenyl phosphite di-iodide. (−)-Octan-2-ol (13 g.; $[\alpha]_D^{27}$ −8·65°) gave (+)-2-iodo-octane (16·6 g., 69%), b. p. 42°/0·5 mm., n_D^{20} 1·4881, $[\alpha]_D^{23}$ +9·53°.

Triphenyl phosphite chlorobromide. (−)-Octan-2-ol (11·7 g.; $[\alpha]_D^{21}$ −9·24°) gave the following fractions: (i) b. p. 46—85°/30 mm., 1·1 g., n_D^{20} 1·4262, $[\alpha]_D^{22}$ +10·90°; (ii) b. p. 85°/30 mm., 2·0 g., n_D^{20} 1·4430, α_D^{22} +21·49°; (iii) b. p. 85—87°/30 mm., 5·2 g., n_D^{20} 1·4468, $[\alpha]_D^{22}$ +22·08°; (iv) b. p. 87°/20 mm., 4·5 g., n_D^{20} 1·4510, α_D^{22} +20·98°; (v) b. p. 87—95°/20 mm., 2·3 g., n_D^{20} 1·4502, α_D^{22} +20·90°. Fraction (i) was practically pure 2-chloro-octane, and fractions (iv) and (v) were somewhat impure 2-bromo-octane. Calculation showed the whole product to contain 2·3 g. (17% yield) of (+)-2-chloro-octane, $[\alpha]_D^{22}$ +10·9°, and 12·7 g. (73% yield) of (+)-2-bromo-octane, $[\alpha]_D^{22}$ +21·2°.

Triphenyl phosphite chloro-iodide. (+)-Octan-2-ol (20 g.; $[\alpha]_D^{22}$ +8·72°) yielded 16·5 g. of almost pure (−)-2-iodo-octane, n_D^{20} 1·4868, $[\alpha]_D^{23}$ −27·46°. On distillation, the first few drops (0·75 g.) which contained all the chloro-octane, had n_D^{23} 1·4569, α_D^{23} −24·78°. Calculation showed that the whole product contained 16·2 g. (47% yield) of (−)-2-iodo-octane, $[\alpha]_D^{23}$ −27·5°, and 0·3 g. (1% yield) of (−)-2-chloro-octane, $[\alpha]_D^{23}$ −23·0°.

Triphenyl phoshite bromo-iodide. (−)-Octan-2-ol (20 g.; $[\alpha]_D^{22}$ −8·81°) gave: (i) b. p. 81—82°/19 mm., 8·7 g., n_D^{23} 1·4500, α_D^{20} +29·56°; (ii) b. p. 82—84°/22 mm., 6·0 g., n_D^{23} 1·4548, α_D^{20} +29·28°; (iii) b. p. 84—86°/22 mm., 4·0 g., n_D^{23} 1·4769, α_D^{20} +25·42°; (iv) b. p. 98—110°/22 mm., 3·0 g., discoloured by iodine. Calculation showed the whole product to contain 15·1 g. (39% yield) of (+)-2-bromo-octane, $[\alpha]_D^{20}$ +26·75°, and 6·6 g. (14% yield) of (+)-2-iodo-octane, $[\alpha]_D^{20}$ +19·25°.

Attempted Exchange Reactions.—n-*Butyl chloride and diphenyl phosphorobromidate.* The dibromide from triphenyl phosphite (62 g., 0·2 mole) was treated, as usual, with anhydrous methanol (6·4 g., 0·2 mole), and the mixture stirred for an hour. After removal of the methyl bromide under reduced pressure, *n*-butyl chloride (18·4 g., 0·2 mole) was added to the residual mixture of phenol and diphenyl phosphorobromidate. The mixture was kept for 75 min. at room temperature; distillation, washing, and redistillation gave only *n*-butyl chloride (16·5 g., 90%) b. p. 72°, n_D^{20} 1·4020.

n-*Butyl iodide and diphenyl phosphorobromidate.* Repetition of the above experiment, with *n*-butyl iodide (35 g.) in place of the chloride, similarly gave only recovered *n*-butyl iodide (29·5 g., 85%), n_D^{20} 1·4945.

*Action of Halogens on Tri-*n-*butyl Phosphite.*—The halogen (0·1 mole) was added dropwise, with stirring, to ice-cooled tri-*n*-butyl phosphite (0·1 mole; b. p. 105—110°/0·5 mm., n_D^{25} 1·4303;

Gerrard, *J.*, 1940, 1464). After 3 hr. at room temperature the product was distilled under reduced pressure into traps cooled to −70°, all material boiling below 100°/20 mm. being collected. The distillate was washed with 10% sodium hydroxide solution and water and dried ($MgSO_4$). The results were :

	Product				Product			
		Yield (mole)				Yield (mole)		
Halogen	n_D^{20}	Bu^{n}Br	Bu^{n}I	Halogen	n_D^{20}	Bu^{n}Cl	Bu^{n}Br	Bu^{n}I
Br_2	1·4389	0·20	—	ICl	1·4731	0·035	—	0·09
I_2	1·4935	—	0·19	IBr	1·4760	—	0·07	0·10

FACULTY OF TECHNOLOGY, UNIVERSITY OF MANCHESTER, MANCHESTER, 1.
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, S. KENSINGTON, LONDON, S.W.7.

[*Received, February 12th*, 1954.]

Nucleotides. Part XXVIII. A Synthesis of Uridine-5′ Triphosphate (UTP).*

By G. W. KENNER, A. R. TODD, R. F. WEBB, and F. J. WEYMOUTH.

[Reprint Order No. 5143.]

Uridine-5′ triphosphate has been synthesised by condensing 2′ : 3′-di-*O*-acetyl- or 2′ : 3′-*O*-*iso*propylidene-uridine-5′ benzyl phosphorochloridate with a salt of tribenzyl pyrophosphate, and then removing the benzyl and other protecting groups. The synthetic product is identical with uridine triphosphate (UTP) (III) isolated from natural sources. The synthesis of uridine-5′ pyrophosphate (UDP) (Kenner, Todd, and Weymouth, *J.*, 1952, 3675) has been improved.

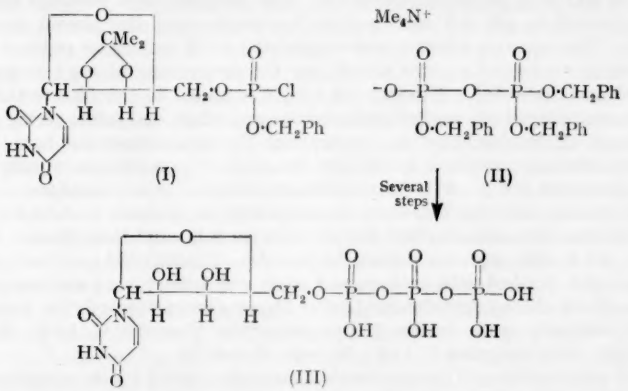
AFTER the isolation of adenosine triphosphate from muscle extracts (Lohmann, *Naturwiss.*, 1929, **17**, 624; Fiske and Subbarow, *Science*, 1929, **70**, 381), various other coenzymes were recognised (*e.g.*, coenzyme I, FAD) as derivatives of adenosine, but until recently no substances of a similar nature were known which were derived from any other natural ribonucleoside. In 1950, however, Caputto, Leloir, Cardini, and Paladini (*J. Biol. Chem.*, 1950, **184**, 333) described the isolation of uridine-diphosphate-glucose (UDPG) which acts as coenzyme in the system which converts galactose into glucose. Since then related compounds have been reported, including uridine-diphosphate-glucuronic acid (Dutton and Storey, *Proc. Biochem. Soc.*, 1953, **53**, xxxvii; Smith and Mills, *Biochem. Biophys. Acta*, 1954, in the press), uridine-diphosphate-*N*-acetylglucosamine (Cabib, Leloir, and Cardini, *J. Biol. Chem.*, 1953, **203**, 1055), and even more complex uridine diphosphate derivatives (Park, *ibid.*, 1952, **194**, 877, 885). Kornberg (*Symp. Phosphorus Metabolism*, 1951, **1**, 392) suggested that uridine-5′ triphosphate (UTP) (III) might be an intermediate in the enzymic synthesis of such uridine derivatives and was indeed able to demonstrate that uridine triphosphate could be prepared enzymically from uridine diphosphate (uridine-5′ pyrophosphate).

As part of our general programme on nucleoside polyphosphate synthesis we prepared uridine-5′ triphosphate in the latter part of 1952. Our immediate object was then to demonstrate the validity of a synthetic method and no serious attempt was made to increase the purity of the final product above about 50%. The material in this state of purity was, however, adequate for biochemical studies, and it was used in investigations which demonstrated the production of urdine-5′ triphosphate by the uridyl transferase-catalysed pyrophosphorolysis of UDPG (Munch-Petersen, Kalckar, Cutolo, and Smith, *Nature*, 1953, **172**, 1036) and from UDPG and uridine-diphosphate-*N*-acetylglucosamine in presence of a rat-liver nuclear fraction (Smith, Munch-Petersen, and Mills, *ibid.*, p. 1038). The growing biochemical interest in uridine triphosphate encouraged us to continue work on its synthesis. Bergkvist and Deutsch (*Acta Chem. Scand.*, 1953, **7**, 1307) meanwhile

* Part XXVII, *J.*, 1954, 1448.

detected uridine triphosphate and guanosine triphosphate in anion-exchange chromatogram fractions of yeast and muscle extracts, and Lipton, Morell, Frieden, and Bock (*J. Amer. Chem. Soc.*, 1953, **75**, 5449) isolated uridine triphosphate in substance from yeast using anion-exchange methods.

The methods employed in this laboratory for the synthesis of adenosine-5′ triphosphate (Part II, Baddiley, Michelson, and Todd, *J.*, 1949, 582; Part IV, Michelson and Todd, *ibid.*, p. 2487) are not readily applicable to the corresponding uridine derivative (cf. Part XV, Anand, Clark, Hall, and Todd, *J.*, 1952, 3665). It was therefore decided to extend the method used by Kenner, Todd, and Weymouth (Part XVII, *ibid.*, p. 3675) for uridine-5′ pyrophosphate (UDP) and to synthesise uridine-5′ triphosphate by condensing a suitable protected derivative of uridine-5′ benzyl phosphorochloridate with a salt of tribenzyl pyrophosphate and subsequently removing the benzyl and other protecting groups. The major difficulty in polyphosphate syntheses of this nature lies in the extreme lability of the fully esterified products obtained after the initial condensation, and the consequent need for a method by which at least partial debenzylation to more stable intermediates can be effected smoothly and rapidly. In the earlier syntheses of uridine-5′ pyrophosphate (Parts XV and XVII, *locc. cit.*) partial debenzylation was effected by lithium chloride, but in the present work we used phenols as debenzylating agents based on as yet unpublished experiments by Dr. A. S. Curry and Mr. J. Mather in this laboratory. In a preliminary experiment, use of this method for the partial debenzylation of tribenzyl 2′ : 3′-*O*-*iso*propylideneuridine-5′ pyrophosphate (Part XVII, *loc. cit.*), followed by hydrogenolysis of remaining benzyl groups and removal of the *iso*propylidene residue with acid, gave considerably improved yields of uridine-5′ pyrophosphate.



Since no information was then available about the stability of uridine triphosphate, 2′ : 3′-di-*O*-acetyluridine was used as starting material, for it could be assumed that mild deacetylation with catalytic amounts of alkali-metal alkoxides would not cause extensive destruction of the triphosphate residue. Accordingly 2′ : 3′-di-*O*-acetyluridine-5′ benzyl phosphite was treated with *N*-chlorosuccinimide and the resulting phosphorochloridate was brought into reaction with triethylammonium tribenzyl pyrophosphate. The resinous product, presumably mainly 2′ : 3′-di-*O*-acetyluridine-5′ tetrabenzyl triphosphate, was partially debenzylated with hot phenol, and the isolated product was deacetylated with sodium methoxide in methanol. The remaining benzyl groups were removed by hydrogenolysis and the crude uridine-5′ triphosphate isolated as a sodium salt. Paper-chromatographic analysis indicated that the main component of the crude product showing ultra-violet absorption (*ca.* 50% of the total absorption at 260 mμ) was uridine-5′ triphosphate, the remainder being uridine-5′ pyrophosphate and uridine-5′ phosphate, doubtless arising by decomposition of initially formed triphosphate. Independent assays of this material by paper chromatography (Smith and Mills, *loc. cit.*) and by biological methods (Berg and Joklik, *Nature*, 1953, **172**, 1008) confirmed our own findings.

From the behaviour of this crude material it was clear that uridine-5′ triphosphate was more stable to acids than we had feared and so for subsequent syntheses we used the more accessible 2′ : 3′-*O-iso*propylideneuridine as starting material. In the final method 2′ : 3′-*O-iso*propylideneuridine-5′ benzyl phosphorochloridate (I) was condensed with the crystalline tetramethylammonium tribenzyl pyrophosphate (II), the product at once partially debenzylated with *m*-cresol containing a little hydrogen chloride, and the removal of benzyl groups then completed by hydrogenolysis. Subsequent removal of the *iso*propylidene residue and precipitation as a lithium salt yielded a material containing *ca.* 37% of uridine-5′ triphosphate (III), the impurities being the 5′-pyrophosphate and 5′-phosphate and inorganic phosphates. Further purification by charcoal chromatography or, much more conveniently, by anion-exchange chromatography (Dowex-2) gave pure uridine-5′ triphosphate which we isolated as the barium salt. Through the courtesy of Dr. S. A. Morell we were able to identify the synthetic product with natural uridine triphosphate by direct comparison with a specimen of the sodium salt isolated in the Pabst Laboratories (Milwaukee) from yeast. The synthetic method described is straightforward in use and on the scale employed has given yields of *ca.* 29% based on uridine.

Experimental

Uridine-5′ Barium Pyrophosphate.—Crude tribenzyl 2′ : 3′-*O-iso*propylidene uridine-5′ pyrophosphate (prepared from 1·94 g. of benzyl 2′ : 3′-*O-iso*propylidene uridine-5′ phosphite; Kenner, Todd, and Weymouth, *J.*, 1952, 3679) and dry phenol (12 g.) were heated at 50° for 17 min. Water (140 c.c.) and ethanol (60 c.c.) were added and the resulting homogeneous solution (approx. N/20) was hydrogenated overnight at atmospheric pressure with a mixture of palladous oxide and 10% palladium–charcoal. The catalysts were removed by filtration, the filtrate was adjusted to pH 4·5 with sodium hydroxide, and the phenol removed in ether (5 × 100 c.c.). The aqueous solution was evaporated to 10 c.c. under reduced pressure (final pH 3·5), barium bromide (1·7 g.) was added, and the precipitate (90 mg.) immediately formed was filtered off and discarded. Ethanol (28 c.c.) was added to the filtrate (18 c.c.), and the precipitate was centrifuged off, washed with acetone and ether, and dried, giving a white powder (1·40 g.). Paper chromatography in *iso*propanol–1% ammonium sulphate solution (3 : 2) showed that this product contained, in addition to uridine-5′ pyrophosphate, only small amounts of uridine-5′ phosphate and 2′ : 3′-*O-iso*propylidene uridine-5′ pyrophosphate.

The above barium salt was dissolved as completely as possible in 0·1N-hydrochloric acid (10 c.c.), the mixture set aside at room temperature for 5 hr. and then filtered, and the filtrate neutralised to pH 6 with aqueous barium hydroxide. Ethanol (30 c.c.) was added, and the precipitate collected, washed with acetone and ether and dried, giving a white powder (0·99 g., 34% based on 2′ : 3′-*O-iso*propylideneuridine). Paper chromatography as before showed the product to be virtually pure uridine-5′ pyrophosphate (Found: C, 15·8; H, 3·1; N, 3·6. $C_9H_{11}O_{12}N_2P_2Ba_{1\frac{1}{2}},5H_2O$ requires C, 15·5; H, 3·0; N, 4·0%).

2′ : 3′-*Di*-O-*acetyluridine.*—Triphenylmethyl chloride (11·4 g.) was added to a solution of uridine (10 g.) in pyridine (100 c.c.). The mixture was kept at room temperature for 2 days and then at 100° for 3 hr. Acetic anhydride (80 c.c.) was added to the cooled solution which, after a further 20 hr., was poured into vigorously stirred ice-water (800 c.c.). The flocculent precipitate was collected and dried (26·4 g.). A mixture of this material and 80% acetic acid (90 c.c.) was boiled under reflux for 7 min. before concentration to small bulk under reduced pressure. Addition of water (200 c.c.) gave a suspension, which was extracted with benzene (3 × 70 c.c.) and then filtered. The aqueous solution was concentrated to 100 c.c. and extracted with ethyl acetate (6 × 30 c.c.), which yielded on evaporation a pale yellow resin (6·4 g.), which slowly crystallised. It was recrystallised by dissolution in the minimum quantity of acetone and addition of ether (2 vols.), followed by sufficient pentane to produce slight turbidity. This *diacetate* (6·05 g., 45%) was used for further work, but the m. p. could be raised by repeated recrystallisation from 133—134° to 142—143° (Found, in material dried at 70°: C, 47·7; H, 5·2; N, 8·6. $C_{13}H_{16}O_8N_2$ requires C, 47·6; H, 4·9; N, 8·5%).

2′ : 3′-*Di*-O-*acetyluridine*-5′ *Benzyl Phosphite.*—Application of the method described by Kenner, Todd, and Weymouth (*loc. cit.*) for the *iso*propylidene compound to 2′ : 3′-di-*O*-acetyluridine (0·90 g.) gave a pale yellow resin, which was purified by pouring a solution in benzene (10 c.c.) into *cyclo*hexane (200 c.c.). The precipitated gum (1·12 g., 85%) appeared to be homogeneous on paper chromatography (R_F 0·78 in *n*-butanol–water) and was converted by

successive chlorination with *N*-chlorosuccinimide, hydrolysis with aqueous sodium hydrogen carbonate, deacetylation with sodium methoxide, and hydrogenolysis into material indistinguishable by paper chromatography in *iso*propanol–1% ammonium sulphate (3 : 2) from uridine-5′ phosphate.

Tetramethylammonium Tribenzyl Pyrophosphate.—Silver tribenzyl pyrophosphate was prepared by the method of Baddiley, Clark, Michalski, and Todd (*J.*, 1949, 818) and recrystallised by adding 5 vols. of water to a filtered solution in the minimum quantity of boiling acetone (Found, in the hygroscopic material dried at 60° : C, 45·0; H, 4·0. Calc. for $C_{21}H_{21}O_7P_2Ag$: C, 45·4; H, 3·8%). To a solution of silver tribenzyl pyrophosphate (5·55 g.) in acetone (200 c.c.) was added one of tetramethylammonium iodide (2·01 g.) in water (100 c.c.). The mixture was refluxed for 5 min., then filtered through "Hyflo Supercel," the filtrate was evaporated to dryness, and the last traces of moisture were removed by repeated evaporation with benzene. The waxy residue on crystallisation from benzene–*cyclo*hexane gave fine, colourless, hygroscopic needles of *tetramethylammonium tribenzyl pyrophosphate* (4·8 g.), m. p. 74—75° (Found, in material dried at room temperature : N, 2·85; P, 11·7. $C_{25}H_{33}O_7NP_2$ requires N, 2·7; P, 11·9%).

Triethylammonium tribenzyl pyrophosphate was similarly prepared by dissolving silver tribenzyl pyrophosphate in chloroform, adding the theoretical quantity of solid triethylammonium chloride, filtering off the precipitated silver chloride, and evaporating *in vacuo*. The triethylammonium salt obtained as a gum was dried before use by repeated evaporation with benzene.

Uridine-5′ Triphosphate.—(*a*) A mixture of benzyl 2′ : 3′-di-*O*-acetyluridine-5′ phosphite (1·95 g.) and *N*-chlorosuccinimide (0·54 g.) in methyl cyanide (12 c.c.) was kept at room temperature for 2 hr. A solution of triethylammonium tribenzyl pyrophosphate (prepared from 2·47 g. of silver tribenzyl pyrophosphate) in methyl cyanide (20 c.c.) was slowly added, followed by a few drops of triethylamine, and the solution was set aside for 2 hr. at room temperature. The solvent was evaporated *in vacuo*, the residue dissolved in molten phenol (25 g.), and the solution heated at 60° for 15 min. Water (100 c.c.) was then added and the solution extracted with ether (200 c.c., then 3 × 100 c.c.). The aqueous solution was neutralised to pH 7·5 with N-sodium hydroxide (1·5 c.c.), evaporated to 70 c.c., and freeze-dried, affording a resin (3·26 g.) which was dissolved in methanol (20 c.c.). A solution of phenolphthalein in methanol (2 drops) was added, followed by sodium methoxide in methanol until a permanent pink colour was obtained. A gel was formed after 5 min., and after 30 min. solid carbon dioxide was added, followed by acetone (20 c.c.). The precipitate was centrifuged off and dissolved in water, and the solution brought to pH 4 with hydrochloric acid and hydrogenated at atmospheric pressure with a mixed palladous oxide–palladised charcoal catalyst. The hydrogen uptake (53 c.c.) was complete in 1·5 hr. The catalyst was filtered off, and the filtrate neutralised to pH 7 with sodium hydroxide, evaporated to 5 c.c., and poured into acetone (40 c.c.). The precipitated oil was centrifuged off and dried under reduced pressure, to give a stable frothy glass (867 mg.). Paper chromatography in *iso*propanol–1% ammonium sulphate solution (3 : 2) showed the nucleotide content of the final product to be approximately : uridine-5′ triphosphate 40—50, pyrophosphate 25—30, and phosphate 25—30%. The ultraviolet absorption at 260 mμ showed that nucleotides accounted for about 72% of the weight of the crude material. The yield of uridine-5′ triphosphate obtained was therefore approx. 12%.

(*b*) A mixture of benzyl 2′ : 3′-*O*-*iso*propylideneuridine-5′ phosphite (3·6 g.) and *N*-chlorosuccinimide (1·18 g.) in benzene (10 c.c.) and methyl cyanide (15 c.c.) was gently stirred at room temperature for 2 hr. A solution of tetramethylammonium tribenzyl pyrophosphate (4·62 g.) in methyl cyanide (20 c.c.) was added and the stirring continued for a further 2½ hr. The mixture was filtered and the precipitate of tetramethylammonium chloride (0·4 g.) was washed with benzene (5 c.c.). The combined filtrate and washings were evaporated *in vacuo*, the residue was dissolved in dry *m*-cresol, and the solution was made up to 100 c.c. with *m*-cresol. To 50 c.c. of the above solution a solution of hydrogen chloride in dry *m*-cresol (5·0 c.c. of 0·5N) was added and the mixture set aside for 2 hr., during which a gelatinous mass separated. Ethanol (55 c.c.) and water (50 c.c.) were added and the resulting homogeneous solution was hydrogenated at atmospheric pressure with a mixed palladium oxide–palladised-charcoal (5%) catalyst. The hydrogenation was interrupted after 3 hr. (uptake 158 c.c.), and the catalyst was filtered off and washed with water (5 c.c.). The combined filtrate and washings were diluted with water (150 c.c.), extracted with ether (4 × 100 c.c.), further diluted with water (to 350 c.c.), and set aside at 5° for 12 hr. The solution was neutralised to pH 7·0 with N-lithium hydroxide (19·3 c.c.), evaporated to 20 c.c. *in vacuo*, and filtered into acetone (220 c.c.). The precipitate

was centrifuged off, washed with acetone (2 × 220 c.c.), then with ether (100 c.c.), and dried over phosphoric oxide *in vacuo*, affording a fine white powder (2·1 g.). The remaining 50 c.c. of the cresol solution of tetrabenzyl uridine-5′ triphosphate, similarly treated, also gave a fine white powder (2·0 g.). Paper chromatography in *iso*propanol–1% ammonium sulphate showed that the material contained uridine-5′ triphosphate (5%) and uridine-5′ diphosphate (5%), together with much material having a negative reaction with a periodate spray (Buchanan, Dekker, and Long, *J.*, 1950, 3162). The total product (4·1 g.) was therefore dissolved in water (160 c.c.), divided into 4 portions of 40 c.c., and each portion in turn was passed through a column (4 × 4 cm.) of cation-exchange resin (Zeocarb 315, H^+ form); the column was washed with water (40 c.c.), and the combined effluents were hydrogenated overnight as above. Filtrate from the catalyst was neutralised with N-lithium hydroxide (9 c.c.). The solutions so obtained were combined, evaporated to small bulk (25 c.c.), and poured into acetone (220 c.c.), and the precipitate was centrifuged off, washed with acetone (2 × 200 c.c.) and with ether (200 c.c.), and dried over phosphoric oxide, yielding a white powder (3·4 g.). Paper chromatography in *iso*propanol–1% ammonium sulphate solution (3 : 2), followed by elution of the spots with 0·01N-hydrochloric acid and determination of the amounts of individual nucleotides by ultra-violet absorption measurements at 260 mμ, gave uridine-5′ triphosphate 41, pyrophosphate 29·4, and phosphate 29·6%. Determination of the ultra-violet absorption of a dilute solution of the product showed that these nucleotides accounted for 74% of the weight of the crude material. The actual yield of uridine-5′ tetralithium triphosphate was thus 1·26 g. (29% from uridine).

Charcoal Chromatography of Uridine-5′ Triphosphate.—A solution of the mixed sodium salts described in (*a*) above (1·17 g., containing approx. 30% of inorganic phosphate and pyrophosphate) in water (50 c.c.) was applied to a column (8 cm. × 4·5 cm. diam.) of charcoal ("Karbak;" 40 g.; previously purified by being washed with 2N-hydrochloric acid, by continuous extraction of the solid with water, ethanol, *iso*propanol and again water, and by drying and activation at 350° for 72 hr.), supported on "Hyflo Supercel" (10 g.). The column was eluted with, successively, water, 15% and 30% aqueous ethanol, and ethanol; the eluant was collected in an automatic fraction collector (9-c.c. fractions; flow rate 1 c.c./1 min.), and the progress of elution followed by paper chromatography in *iso*propanol–1% ammonium sulphate (3 : 2). With water elution, fractions 11—20 contained only inorganic pyrophosphate (eluant pH 2); fractions 21—50 contained only pyrophosphate and uridine triphosphate (pH 2, rising to 5); fractions 51—135 contained only uridine triphosphate; fractions 136—230 contained only traces of ultra-violet absorbing material. Subsequent elution with aqueous ethanol gave solutions containing uridine mono-, di-, and tri-phosphates. Fractions 60—90 from the water elution described above were pooled, neutralised to pH 6 with N-sodium hydroxide, evaporated to small bulk, and finally freeze-dried. The residue was dissolved in water (0·8 c.c.), the solution filtered into ethanol (4 c.c.), and the precipitate centrifuged off. This was examined by paper chromatography (see below). To a solution of the precipitate in 0·05N-hydrochloric acid (4 c.c.) was added barium acetate (0·5 c.c. of a saturated solution), and the precipitate was centrifuged off, washed with water (2 × 1·5 c.c.), ethanol (2 × 1·5 c.c.), and ether (2 × 1·5 c.c.), and dried *in vacuo* over phosphoric oxide, to give *uridine-5′ barium triphosphate* (27 mg.) as a fine white powder [Found, in material dried over phosphoric oxide at 0·1 mm.: C, 15·3; H, 2·3; N, 3·5; P, 12·8%; total P/acid-labile P, 1·49/1. $(C_9H_{12}O_{15}N_2P_3)_2Ba_3,4H_2O$ requires C, 14·95; H, 2·2; N, 3·9; P, 12·85%; total P/acid-labile P, 1·5/1]. Phosphate analysis by Allen's method (*Biochem. J.*, 1940, **34**, 858) showed a negligible amount (0·25%) of orthophosphate to be present.

Identification of the Synthetic Uridine-5′ Triphosphate with a Specimen isolated from Yeast.—The synthetic sodium uridine-5′ triphosphate isolated by elution from a charcoal column (see above) and a sample isolated by anion-exchange from yeast extracts supplied by Dr. S. A. Morell were run side by side on Whatman No. 1 paper, using three solvent systems.

	Migration (cm.) (descending)		R_P (ascending)
	A	B	C
Synthetic uridine-5′ triphosphate	1·8	14·6	0·1
Natural uridine-5′ triphosphate	1·8	14·8	0·1
Synthetic barium uridine-5′ pyrophosphate	3·3	16·5	0·16
Barium uridine-5′ phosphate	8·0	20·0	0·20

Solvent systems: A, 95% ethanol (5)–M-ammonium acetate, pH 7 (2), run for 52 hr.; B, *iso*propanol (3)–1% ammonium sulphate solution (2), run for 20 hr. on paper previously soaked in 1% ammonium sulphate solution and dried; C, *n*-butanol (6)–acetic acid (2)–water (3).

Anion-exchange Chromatography of Uridine-5′ Triphosphate.—A solution of the lithium salt (1·5 g.) from preparation (*b*) above in water (200 c.c.) was brought on to a column (5 × 3 cm.) of Dowex-2 resin (chloride form). Uridine-5′ phosphate, uridine-5′ pyrophosphate and inorganic phosphate were eluted by a sodium chloride (0·1N)–hydrochloric acid (0·01N) solution (8 l.). Uridine-5′ triphosphate was then eluted by a sodium chloride (0·2N)–hydrochloric acid (0·01N) solution (7 l.), and finally with N-sodium chloride–0·02N-hydrochloric acid (1 l.). The combined eluates containing uridine-5′ triphosphate were adjusted to pH 7·5 with sodium hydroxide solution, diluted to 24 l., and passed through a column (0·5 × 6·2 cm.) of Dowex-2 resin (chloride form). The column was washed with 0·05N-lithium chloride (50 c.c.), and uridine-5′ triphosphate eluted with ice-cold N-hydrochloric acid (80 c.c.). The eluate was rapidly adjusted to pH 5 with N-lithium hydroxide and evaporated to 40 c.c. A saturated solution of barium acetate (0·4 g.) was added, followed by 0·18N-barium hydroxide solution to pH 6·0. The precipitate formed was centrifuged off, washed with water (2 × 20 c.c.), ethanol (2 × 30 c.c.), and ether (2 × 30 c.c.), and dried *in vacuo* over phosphoric oxide, yielding pure uridine-5′ barium triphosphate (498 mg.) as a stable white powder identical with the product obtained by charcoal chromatography. Addition of an equal volume of ethanol to the supernatant solution from the above precipitation gave a further precipitate which was similarly washed with water, ethanol, and ether and dried, giving a further quantity of the barium salt (148 mg.).

Our thanks are offered to the Ramsay Memorial Trustees for a Fellowship (to R. F. W.), to the Department of Scientific and Industrial Research for a Maintenance Allowance (to F. J. W.), and to the Rockefeller Foundation for grants.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 22nd,* 1954.]

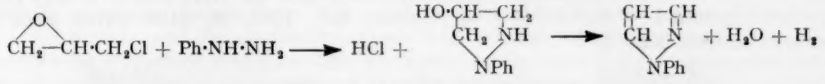
The Preparation and Properties of Some Derivatives of 1-*Phenylpyrazole.*

By I. L. FINAR and K. E. GODFREY.

[Reprint Order No. 5184.]

The preparation of 1-phenylpyrazole from epichlorohydrin and phenylhydrazine has been improved, and the method has been extended to include the use of nitrophenylhydrazines. Some 4-substituted derivatives of 1-phenylpyrazole have been prepared, and their properties have been investigated.

1-PHENYLPYRAZOLE is best prepared by a modification of Balbiano's method (*Gazzetta*, 1887, **17**, 177; 1889, **19**, 128); yield was raised from 58 to 72% (cf. Stoermer and Martinsen, *Annalen*, 1907, **352**, 333; Knorr and Laubman; *Ber.*, 1889, **22**, 180; Claisen, *Ber.*, 1903, **36**, 3664; Alvisi, *Gazzetta*, 1892, **22**, 158); 4-hydroxy-1-phenylpyrazolidine is known to be an intermediate (Gerhard, *Ber.*, 1891, **24**, 352), and we have shown that, when heated to 150°, the latter decomposes to give 1-phenylpyrazole:



The corresponding two *p*-tolyl compounds were similarly prepared, but pyrazolidines could not be obtained in the preparation of 1-*o*-tolyl-, 1-*m*-nitrophenyl-, or 1-*p*-nitrophenylpyrazole.

Attempts to prepare 1-*o*-nitrophenyl- and 1-(2 : 4-dinitrophenyl)-pyrazole (Copenhaver, U.S.P. 2,515,160; 2,527,533) failed. Balbiano's original method gave better yields of *o*- and *p*-tolylpyrazole (*Gazzetta*, 1888, **18**, 362, 368) than our modified method, and so was used for 1-*m*-tolylpyrazole.

Chloromethylation of 1-phenylpyrazole, best carried out in boiling ligroin by Blanc's

method (*Bull. Soc. chim.*, 1923, **33**, 313) using zinc chloride and sulphuric acid, gave the 4-chloromethyl derivative. Reaction in aqueous media (Cambron, *Canad. J. Res.*, 1939, **17**, *B*, 10) and working up with propanol (Dvoretzky and Richter, *J. Org. Chem.*, 1950, **15**, 1285), gave 4-chloromethyl-1-phenylpyrazole and 1-phenyl-4-propoxymethylpyrazole, with smaller amounts of di-(1-phenyl-4-pyrazolyl)methane and di-(1-phenyl-4-pyrazolylmethyl) ether. The propoxymethyl compound was also obtained by heating the chloromethyl compound with propanol; this unusual reactivity of the chloromethyl group (cf. 1-benzyl-4-chloromethylpyrazole hydrochloride; Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 3994) is confirmed by hydrolysis of 4-chloromethyl-1-phenylpyrazole with boiling water to the pyrazolylmethyl ether as sole product. This ether is obtained by self-condensation of 4-hydroxymethyl-1-phenylpyrazole (prepared from its acetyl derivative) in the presence of zinc chloride and sulphuric acid or by heating the hydroxymethyl compound with 4-chloromethyl-1-phenylpyrazole, and the last reaction presumably occurs during the hydrolysis by water.

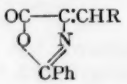
Although obtained in the aqueous chloromethylations, di-(1-phenyl-4-pyrazolyl)-methane was not formed under anhydrous conditions. It was, however, formed by heating 1-phenylpyrazole in water with paraformaldehyde (no hydrochloric acid), 4-chloromethyl-1-phenylpyrazole, or 4-hydroxymethyl-1-phenylpyrazole: 1-phenylpyrazole fails to condense with its 4-chloromethyl derivative in ligroin, where no hydrolysis is possible, so that the hydroxymethyl compound is probably an intermediate in the formation of di-(1-phenyl-4-pyrazolyl)methane (cf. Elderfield, " Heterocyclic Compounds," John Wiley and Sons, Inc., New York, 1950, Vol. I, p. 318; Stephen, Short, and Gladding, *J.*, 1920, **117**, 511).

The dipyrazolylmethane was oxidised by alkaline permanganate to di-(1-phenyl-4-pyrazolyl) ketone; the homologue, di-(1-phenyl-4-pyrazolyl)ethane, was prepared from 4-chloromethyl-1-phenylpyrazole by the Wurtz reaction. The chloromethyl compound was oxidised by alkaline permanganate to 1-phenylpyrazole-4-carboxylic acid, apparently the best route to the acid (cf. Balbiano and Marchetti, *Gazzetta*, 1893, **23**, 484; Claisen, *Annalen*, 1897, **295**, 319; Wislicenus and Bindemann, *Annalen*, 1901, **316**, 36; Dyer and Johnson, *J. Amer. Chem. Soc.*, 1934, **56**, 223; Panizzi, *Gazzetta*, 1946, **76**, 56).

Attempts to prepare 4-cyanomethyl-1-phenylpyrazole from the chloromethyl compound failed.

By the Sommelet reaction (Sommelet, *Compt. rend.*, 1913, **157**, 852; Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2144), 4-chloromethyl-1-phenylpyrazole was converted into 4-formyl-1-phenylpyrazole, which was converted into the acid by permanganate, and by the Cannizzaro reaction (Cannizzaro, *Annalen*, 1853, **88**, 129) gave 4-hydroxymethyl-1-phenylpyrazole and 1-phenylpyrazole-4-carboxylic acid; by the Doebner modification of the Knoevenagel condensation (Doebner, *Ber.*, 1900, **33**, 2140) or by the Perkin reaction (Kalnin, *Helv. Chim. Acta*, 1928, **11**, 977) it gave β-(1-phenyl-4-pyrazolyl)acrylic acid.

The Erlenmeyer azlactone condensation with hippuric acid (Kropp and Decker, *Ber.*, 1909, **42**, 1184) gave 2-phenyl-4-(1-phenyl-4-pyrazolylmethylene)oxazol-5-one (I), reduced by red phosphorus and hydriodic acid (Gillespie and Snyder, *Org. Synth.*, 1934, **14**, 80) to α-amino-β-(1-phenyl-4-pyrazolyl)propionic acid (II). The pyrazole-aldehyde condenses with acetone to form 4-(1-phenyl-4-pyrazolyl)but-3-en-2-one (III) and 1 : 5-di-(1-phenyl-4-pyrazolyl)penta-1 : 4-dien-3-one (IV) (Claisen, *Ber.*, 1881, **14**, 2468, 2470), even when excess of acetone is used.



(I)

$HO_2C{\cdot}CH(NH_2){\cdot}CH_2R$ (II)

$CH_3{\cdot}CO{\cdot}CH{:}CHR$ (III)

$R{\cdot}CH{:}CH{\cdot}CO{\cdot}CH{:}CHR$ (IV)

R =

4-Acetoxymercuri-1-phenylpyrazole was prepared by direct mercuration of the pyrazole (cf. Paolini and Silbermann, *Gazzetta*, 1915, **45**, II, 385), and was orientated by conversion into 4-bromo-1-phenylpyrazole (Balbiano, *Gazzetta*, 1889, **19**, 128). The acetoxymercuri-compound with sodium chloride in aqueous acetic acid (Whitmore and Hanson, *Org. Synth.*, 1925, **4**, 13) gave 4-chloromercuri-1-phenylpyrazole, similarly converted into 4-bromo-1-phenylpyrazole. The chloromercuri-compound was also

prepared directly with mercuric chloride (cf. Gilman and Wright, *J. Amer. Chem. Soc.*, 1933, **55**, 302). Both mercuri-compounds regenerated 1-phenylpyrazole on treatment with dilute hydrochloric acid (cf. Dimroth, *Ber.*, 1899, **32**, 759).

1-Phenyl-4-thiocyanatopyrazole was obtained by the action of thiocyanogen on either of the mercuri-compounds (cf. Söderbäck, *Annalen*, 1919, **419**, 217), but direct thiocyanation of 1-phenylpyrazole (cf. Kaufmann and Liepe, *Ber.*, 1923, **56**, 2514) gave only thiocyanogen polymers. Reduction of the thiocyano-compound with zinc and acetic acid produced an oil with a thiol odour, which with benzyl chloride produced 4-benzylthio-1-phenylpyrazole.

Even under forcing conditions, with methylmagnesium iodide (de Jonge, den Hertog, and Wibaut, *Rec. Trav. chim.*, 1951, **70**, 989), 4-chloromethyl-1-phenylpyrazole gave no Grignard compound. Under similar conditions, however, 4-bromo-1-phenylpyrazole gave a small yield of the Grignard compound, as indicated by its conversion into 1-phenylpyrazole-4-carboxylic acid on treatment with carbon dioxide.

Experimental

Light petroleum was material of b. p. 40—60°, ligroin had b. p. 90—100°.

1-*Phenylpyrazole.*—To epichlorohydrin (40 g.) in 60% ethanol (150 c.c.) contained in a 2-l. flask was added phenylhydrazine (95 g.). The mixture was warmed cautiously on the steam-bath until the vigorous reaction began (external cooling then necessary), then, when the reaction subsided, refluxed for 1 hr. The solvent was then evaporated, and the residue heated at 170° (bath). After about 30 min. the solid mass changed to a dark brown liquid and a vigorous reaction set in, with evolution of water and ammonia. Removal of the bath was necessary at this stage to moderate the reaction; after the reaction had subsided, the bath was replaced and the temperature was raised to 200° for a further 10 min. Water (1·5 l.) was added, and the mixture was extracted 7—8 times with ether. After removal of the ether, vacuum-distillation gave aniline (32 g.), b. p. 30—58°/0·01 mm., and 1-phenylpyrazole (44·9 g., 72%), b. p. 58—62°/0·01 mm. The aniline may also be removed by washing with a large amount of N-hydrochloric acid.

4-*Hydroxy*-1-*phenylpyrazolidine.*—Phenylhydrazine (10 g.) and epichlorohydrin (4·2 g.) were refluxed in dry benzene (40 c.c.) for 4 hr. The liquid was cooled and filtered, and the filtrate evaporated to small bulk. This was washed with N-hydrochloric acid, and the residual benzene was then evaporated. Recrystallisation of the solid residue from benzene (charcoal) gave the pyrazolidine (0·95 g., 12·6%), m. p. 99—101°. Repeated recrystallisation gave very pale yellow needles, m. p. 102—103° (Gerhard, *loc. cit.*, gives m. p. 103—104°). When this was heated at 150° for a few minutes, 1-phenylpyrazole was obtained.

4-*Hydroxy*-1-p-*tolylpyrazolidine.*—A similar procedure gave 4-*hydroxy*-1-p-*tolylpyrazolidine* (7·2%), pale yellow plates, m. p. 107—108° (Found: C, 67·9; H, 7·1. $C_{10}H_{14}ON_2$ requires C, 67·5; H, 7·8%). At 150° this gave 1-*p*-tolylpyrazole, characterised as the 4-*bromo*-derivative, colourless needles (from ethanol), m. p. 90·5—91° (Found: N, 12·1; Br, 33·8. $C_{10}H_9N_2Br$ requires N, 11·8; Br, 33·75%).

1-*Nitrophenylpyrazoles.*—Equimol. quantities of *p*- or *m*-nitrophenylhydrazine and epichlorohydrin were refluxed in absolute ethanol for about 12 hr. After evaporation of the alcohol, the residue was heated in a bath, the temperature of which was raised from 120° to 170° during 1 hr. for the *m*-isomer, but to 140° for the *p*-isomer. The bath was removed when necessary to control the reaction. The residue was cooled and extracted several times with hot ethyl acetate, and the combined extracts were washed with 7N-hydrochloric acid. The extracts were evaporated, and the residue was heated on the water-bath to remove nitrobenzene. The residual solid was then crystallised, to give 1-m-*nitrophenylpyrazole* (20%), pale yellow rhombs (from benzene–light petroleum and charcoal), m. p. 94·5—95° (Found: C, 57·3; H, 3·7; N, 21·9. $C_9H_7O_2N_3$ requires C, 57·2; H, 3·7; N, 22·2%), or 1-*p*-nitrophenylpyrazole (42%), pale yellow rhombs (from ethyl acetate), m. p. 169·5—170° (D'Alcontres, *Gazzetta*, 1950, **80**, 441, gives m. p. 168·5—169°) (Found: C, 57·1; H, 3·8; N, 22·0%).

4-*Chloromethyl*-1-*phenylpyrazole.*—A mixture of 1-phenylpyrazole (21·6 g.), paraformaldehyde (7·5 g.), pulverised anhydrous zinc chloride (2·0 g.), and concentrated sulphuric acid (2 drops) was mechanically stirred in refluxing ligroin (250 c.c.), and a stream of dry hydrogen chloride was passed in for 90 min. The ligroin was decanted, and the residue refluxed with 10 × 30 c.c. portions of benzene; the benzene extracts were added to the ligroin, and the whole was washed

with aqueous sodium hydrogen carbonate. Distillation under reduced pressure gave 1-phenylpyrazole (0·8 g.), b. p. 60—107°/0·03 mm., and 4-chloromethyl-1-phenylpyrazole (16·5 g.; 57%), b. p. 108—110°/0·03 mm., white plates (from benzene–light petroleum), m. p. 68—69° (Found: C, 61·6; H, 4·4; N, 14·9; Cl, 18·7. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7; N, 14·55; Cl, 18·45%). The compound gradually decomposes in a stoppered bottle. When refluxed with alkaline permanganate the chloromethyl compound (0·4 g.) gave 1-phenylpyrazole-4-carboxylic acid (0·37 g., 95%), colourless needles (from water), m. p. 221—223°; its methyl ester formed colourless needles (from methanol), m. p. 127—128·5°.

4-Hydroxymethyl-1-phenylpyrazole.—The chloromethyl compound (2·0 g.) and silver acetate (1·74 g.) were refluxed in glacial acetic acid (275 c.c.) until the precipitate coagulated. *4-Acetoxymethyl-1-phenylpyrazole* (2·0 g., 89%) was obtained; recrystallisation gave colourless plates (from light petroleum), m. p. 41·5—42° (Found: N, 12·6. $C_{12}H_{12}O_2N_2$ requires N, 13·0%). Hydrolysis with aqueous potassium carbonate gave the *4-hydroxymethyl* compound (1·2 g., 74%), colourless needles (from benzene–light petroleum), m. p. 60·5—61° (Found: C, 68·5; H, 5·85; N, 15·5. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·75; N, 16·1%). The *p-nitrobenzoyl* derivative crystallised in colourless needles (from ethanol), m. p. 153—154° (Found: N, 12·5. $C_{17}H_{13}O_4N_3$ requires N, 13·0%).

Di-(1-phenyl-4-pyrazolylmethyl) Ether.—Equimol. quantities of the 4-hydroxymethyl and the 4-chloromethyl compound were heated on the steam-bath for 5 min., the oil solidifying. The *ether* (43%) was obtained as colourless plates (from benzene), m. p. 168—168·5° (Found: C, 72·6; H, 5·85; N, 17·1. $C_{20}H_{18}ON_4$ requires C, 72·7; H, 5·45; N, 17·0%). It was also prepared by heating for 1 hr. the 4-hydroxymethyl compound in ligroin in the presence of zinc chloride and sulphuric acid; the ether (31%) crystallised on cooling.

Di-(1-phenyl-4-pyrazolyl)ethane.—4-Chloromethyl-1-phenylpyrazole (1·92 g.) was refluxed for 5 hr. in dry ether (30 c.c.) with sodium (0·46 g.). *Di-(1-phenyl-4-pyrazolyl)ethane* (0·2 g., 12·7%) crystallised in colourless needles (from benzene–ligroin), m. p. 120·5—121·5° (Found: C, 76·4; H, 5·65; N, 17·4. $C_{20}H_{18}N_4$ requires C, 76·4; H, 5·7; N, 17·8%).

1-Phenyl-4-propoxymethylpyrazole.—The chloromethyl compound (0·5 g.) was refluxed for 2 hr. in *n*-propanol (10 c.c.), giving the *propoxymethyl* derivative (0·45 g., 80%), m. p. 36—37°, b. p. 96°/0·05 mm. (Found: C, 72·4; H, 7·5; N, 12·7. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 12·95%).

Di-(1-phenyl-4-pyrazolyl)methane.—A mixture of 1-phenylpyrazole (8·64 g.), paraformaldehyde (2·4 g.), water (25 c.c.), phosphoric acid (*d* 1·75; 12 c.c.), and glacial acetic acid (20 c.c.) was heated on the water-bath for 12 hr., cooled, and diluted with water (1·2 l.). The solid (2·05 g.) was filtered off; the filtrate on evaporation under reduced pressure to half its bulk gave a further 1·25 g. of the solid. The combined product was washed with sodium carbonate solution and dried; on crystallisation from ligroin (charcoal), 1·8 g. of white crystals, m. p. 85—95°, were obtained. This product was distilled under reduced pressure, to give 1·3 g. of a product melting above 100°, b. p. 300—305°/10 mm. On crystallisation, first from ligroin (charcoal), and then from methanol (charcoal), *di-(1-phenyl-4-pyrazolyl)methane* was obtained as white needles (0·9 g., 10%), m. p. 113—114°. Repeated crystallisation gave colourless needles, m. p. 115—116° (Found: C, 75·75; H, 5·17; N, 19·1. $C_{19}H_{16}N_4$ requires C, 76·0; H, 5·33; N, 18·7%).

Di-(1-phenyl-4-pyrazolyl) Ketone.—The methane derivative (1·1 g.) was refluxed with alkaline permanganate for 3 hr., thereby giving the *ketone* (0·52 g., 45%), colourless needles (from benzene), m. p. 221° (Found: C, 72·1; H, 4·6; N, 18·1. $C_{19}H_{14}ON_4$ requires C, 72·6; H, 4·45; N, 17·8%). The *oxime* crystallised in white rosettes (from alcohol), m. p. 149·5—150° (Found: C, 69·0; H, 4·8; N, 21·2. $C_{19}H_{15}ON_5$ requires C, 69·3; H, 4·55; N, 21·3%).

4-Formyl-1-phenylpyrazole.—The general method of Angyal *et al.* (*loc. cit.*) was followed, using 4-chloromethyl-1-phenylpyrazole (8·8 g.). The *aldehyde* (5·65 g., 76·5%) was obtained as colourless needles (from aqueous ethanol), m. p. 85° (Found: C, 69·3; H, 4·5; N, 16·7. $C_{10}H_8ON_2$ requires C, 69·8; H, 4·65; N, 16·3%). The *oxime* formed needles (from aqueous ethanol), m. p. 167—167·5° (Found: N, 22·5. $C_{10}H_9ON_3$ requires N, 22·7%), and the *anil* colourless prisms (from ligroin), m. p. 120·5—121° (Found: N, 16·6. $C_{16}H_{13}N_3$ requires N, 17·0%). Oxidation of the aldehyde with alkaline permanganate gave 1-phenylpyrazole-4-carboxylic acid (73%), m. p. 221—222°.

Cannizzaro Reaction with the Aldehyde.—The aldehyde (1·7 g.) was kept at room temperature for 65 hr. in a solution of potassium hydroxide (6 g.) in water (6 c.c.). The product was extracted with ether, and by exhaustive extraction of the ethereal solution with sodium hydrogen sulphite solution the bisulphite compound of the unchanged aldehyde (0·54 g.) was

precipitated, and was filtered off. The ether filtrate gave 4-hydroxymethyl-1-phenylpyrazole (0·35 g.), m. p. 59—60°. The alkaline portion, on acidification, gave 1-phenylpyrazole-4-carboxylic acid (0·6 g.), m. p. 217—219°.

β-(1-*Phenyl*-4-*pyrazolyl*)*acrylic Acid.*—The aldehyde (0·85 g.) was heated at 85° for 1 hr. with malonic acid (1·04 g.) in pyridine (4 c.c.) and piperidine (0·01 c.c.) (all dry) and then the solution was refluxed for 2 hr. The crude *acrylic acid* was obtained by acidification with dilute hydrochloric acid; it gave colourless needles (0·77 g., 73%), m. p. 185—186°, from aqueous acetic acid. Repeated crystallisation raised the m. p. to 186—187° (Found: C, 67·1; H, 4·7; N, 12·6. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%). The acid was also obtained by heating the aldehyde (0·85 g.) with fused potassium acetate (0·77 g.) in acetic anhydride (0·71 c.c.) at 160° for 1 hr., and then at 175—180° for 3 hr. The acrylic acid (0·36 g., 34%), m. p. 185—186°, was obtained by extracting the product with aqueous sodium carbonate, acidifying, and crystallising the precipitate from aqueous acetic acid.

2-*Phenyl*-4-(1-*phenyl*-4-*pyrazolylmethylene*)*oxazol*-5-*one* (I).—The aldehyde (0·43 g.), hippuric acid (0·45 g.), and fused sodium acetate (0·41 g.) were refluxed in acetic anhydride (1·4 c.c.) for 1 min., and then heated on the steam-bath for 30 min. The mixture was kept overnight with excess of cold water, and the crude *oxazolone* was filtered off. Recrystallisation (from benzene–light petroleum) gave fine, yellow needles (1·1 g., 71%), m. p. 182·5—183° (Found: C, 72·9; H, 4·3; N, 13·0. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·1; N, 13·3%).

α-*Amino*-β-(1-*phenyl*-4-*pyrazolyl*)*propionic Acid* (II).—The oxazolone was reduced with red phosphorus and hydriodic acid, according to the method of Gillespie and Snyder (*loc. cit.*). The precipitated *amino-acid* (0·28 g., 61%) had m. p. 241—242° (decomp.); crystallisation gave colourless leaflets (from water), m. p. 242—243° (decomp.) (Found: C, 62·7; H, 6·1; N, 17·8. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

Condensation of the Aldehyde with Acetone.—The aldehyde (1·72 g.) was dissolved in warm acetone (4·0 c.c.); 12% aqueous sodium hydroxide (0·5 c.c.) was added, and the liquid was warmed to 45°, then kept at room temperature for 24 hr. Ethanol was added, and the solid was filtered off and washed several times with ethanol, and then with water; recrystallisation from chloroform–ethyl acetate gave 1 : 5-*di*-(1-*phenyl*-4-*pyrazolyl*)*buta*-1 : 4-*dien*-3-*one* (IV), pale yellow needles, m. p. 240° (0·36 g., 10%) (Found: C, 74·7; H, 4·9; N, 15·4. $C_{23}H_{18}ON_4$ requires C, 75·4; H, 4·9; N, 15·3%). The original filtrate and washings were further diluted with water, and the precipitate filtered off. The solid was extracted with hot ligroin, and, on cooling, the extract deposited yellow crystals, m. p. 81—82° (0·54 g.). After two more crystallisations from ligroin, 4-(1-*phenyl*-4-*pyrazolyl*)*but*-3-*en*-2-*one* (III) was obtained as pale yellow needles, m. p. 92—93° (0·25 g., 12%). By two further crystallisations the m. p. was raised to 95° (Found: C, 73·6; H, 5·9; N, 13·2. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·65; N, 13·2%).

4-*Acetoxymercuri*-1-*phenylpyrazole.*—1-Phenylpyrazole (8·64 g.) and mercuric acetate (19·1 g.) were heated at 90° for 15 min. in acetic acid (75 c.c.); water (30 c.c.) was then added, and the solution was left to crystallise, giving the *acetoxymercuri*-compound (17·5 g., 72·5%), colourless needles, m. p. 191° (Found: Hg, 50·05. $C_{11}H_{10}O_2N_2Hg$ requires Hg, 49·85%). A suspension of the mercuri-compound in chloroform, on treatment with bromine in chloroform, gave 4-bromo-1-phenylpyrazole, m. p. 80—81°. When distilled with dilute hydrochloric acid, the acetoxymercuri-compound gave 1-phenylpyrazole (80%).

4-*Chloromercuri*-1-*phenylpyrazole.*—A solution of sodium chloride (0·33 g.) in 50% aqueous acetic acid (20 c.c.) was added to a solution of the acetoxymercuri-compound (2·2 g.) in the same solvent (70 c.c.) at 90°. The precipitated *chloromercuri*-compound (1·55 g., 75%) crystallised from xylene in colourless needles, m. p. 226° (Found: Cl, 8·9; Hg, 52·5. $C_9H_7N_2ClHg$ requires Cl, 9·4; Hg, 52·9%). 4-Bromo-1-phenylpyrazole, m. p. 80—81°, was obtained by treatment of a suspension of the mercury compound in acetic acid with bromine at room temperature. The chloromercuri-compound gave 1-phenylpyrazole (69%) on distillation with dilute hydrochloric acid.

1-*Phenyl*-4-*thiocyanatopyrazole.*—Bromine (1·6 g.) was added to a suspension of lead thiocyanate (3·3 g.) in dry ether (20 c.c.); the resulting thiocyanogen solution was filtered into a suspension of the 4-acetoxymercuri-compound in dry ether (30 c.c.). The mixture was set aside for 3 hr.; the solid was then filtered off and washed with ether. The combined filtrates were evaporated under reduced pressure at room temperature, and the residue kept for a few days. The yellow crystals were extracted with ether, and the residue was discarded; after concentration, the ethereal solution crystallised, giving 1-*phenyl*-4-*thiocyanatopyrazole* (0·35 g., 18%), m. p. 60—62°. After several crystallisations from ether, white prisms, m. p. 62°, were

obtained (Found : C, 59·1; H, 3·35; N, 21·4; S, 16·4. $C_{10}H_7N_3S$ requires C, 59·7; H, 3·48; N, 20·9; S, 15·9%).

4-Benzylthio-1-phenylpyrazole.—A solution of thiocyanogen in acetic acid was added to a suspension of 4-chloromercuri-1-phenylpyrazole in acetic acid, then set aside for 24 hr. before filtration. The filtrate was boiled with zinc dust for 2·5 hr., filtered, diluted with water, and extracted with ether. Evaporation gave a mixture of oil and crystals; the oil was dissolved in aqueous ethanol, and treated with sodium carbonate and sodium dithionite at 90°. Benzyl chloride was added, and the solution was cooled; the *4-benzylthio-1-phenylpyrazole* was filtered off and recrystallised from ethanol, giving colourless leaflets, m. p. 84·5—85° (Found : N, 9·9; S, 11·3. $C_{16}H_{14}N_2S$ requires N, 10·5; S, 12·0%).

One of us (K. E. G.) gratefully acknowledges the award of the William Gilles Research Fellowship by the Clothworkers' Company.

THE NORTHERN POLYTECHNIC, HOLLOWAY ROAD, LONDON, N.7. [*Received, March 6th*, 1954.]

12-*Oxygenated Pregnane Derivatives. Part III.* Ketals of* allo*Pregnane*-12 : 20-*diones.*

By (MRS.) W. J. ADAMS, D. N. KIRK, D. K. PATEL, V. PETROW, and (MRS.) I. A. STUART-WEBB.

[Reprint Order No. 5190.]

17α-Hydroxy*allo*pregnane-12 : 20-diones undergo ethylene ketal formation exclusively at $C_{(12)}$ differing from analogous 11 : 20-diones which undergo this reaction at $C_{(20)}$.

IN work leading to the preparation of 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (Part II) * we had occasion to prepare some ethylene ketals of *allo*pregnane-12 : 20-diones. The results obtained form the subject of the present communication.

The conversion of an isolated 20-carbonyl group into the cyclic ketal has previously been recorded. Rosenkranz, Pataki, and Djerassi (*J. Org. Chem.*, 1952, **17**, 290) converted 3α-acetoxypregnane-11 : 20-dione smoothly into the 20-ethylene ketal by heating it with ethylene glycol and toluene-*p*-sulphonic acid in benzene. The introduction of a 16α : 17α-epoxy-residue or of a 17α-hydroxyl group into this system exerts little, if any, effect on ketal formation (cf. Julian, " Recent Progress in Hormone Research," Academic Press Inc., 1951, Vol. VI, p. 202), which is, however, completely suppressed by a 21-acetoxyl residue (Antonucci, Bernstein, Lenhard, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1369). Hydrolysis of the last group removes the steric factors inhibiting ketal formation, cortisone, for example, passing readily into a 3 : 20-di(ethylene ketal), which undergoes selective hydrolysis to the 3-ketone on treatment with 90% acetic acid (Antonucci, Bernstein, Heller, Lenhard, Littell, and Williams, *ibid.*, 1953, **18**, 70).

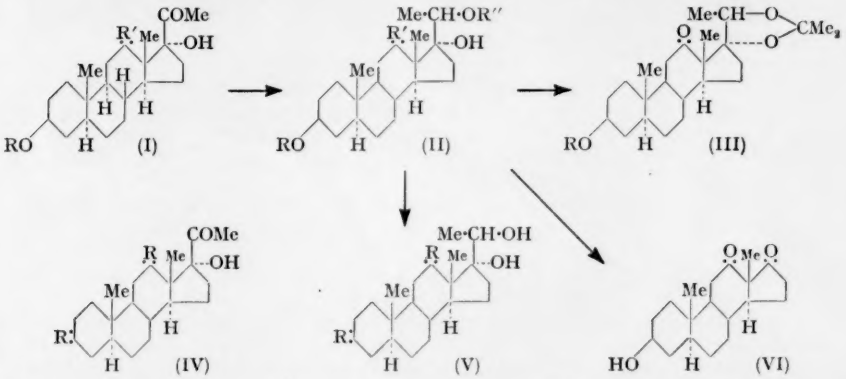
We now find that 3β : 17α-dihydroxy*allo*pregnane-12 : 20-dione (I; R = H, R′ = O) forms only a monoketal on treatment with ethylene glycol and toluene-*p*-sulphonic acid under the usual conditions, or preferably on dissolution in the glycol to which is subsequently added some boron trifluoride–ether complex. The constitution of 12 : 12-ethylenedioxy-3β : 17α-dihydroxy*allo*pregnan-20-one (I; R = H, R′ = ·O·CH_2·CH_2·O·) is assigned to this compound on the basis of the following evidence.

Reduction of the ketal with sodium borohydride leads to the formation of 12 : 12-ethylenedioxy*allo*pregnane-3β : 17α : 20ξ-triol (II; R = R″ = H, R′ = ·O·CH_2·CH_2·O·), hydrolysed by 90% acetic acid to 3β : 17α : 20ξ-trihydroxy*allo*pregnan-12-one (II; R = R″ = H, R′ = O), which was characterised as the 3 : 20-diacetate. Attempts to effect the hydrolysis by the toluene-*p*-sulphonic acid–acetone method of Djerassi, Batres, Romo, and Rosenkranz (*J. Amer. Chem. Soc.*, 1952, **74**, 3634) led to the *iso*propylidene derivative of the foregoing hydrolytic product. The constitution of this hydrolytic product is conse-

* Part II, *J.*, 1954, 2209.

quently that of a 17α : 20ξ-diol, the alternative formulation of a 12β : 17α-diol-20-one being excluded by the stereochemical impossibility of forming an *iso*propylidene link between a 12β- and a 17α-hydroxyl group. The conclusion thus reached was established beyond reasonable doubt by oxidation of (II; R = R″ = H, R′ = O) with sodium bismuthate (Norymberski, *Biochem. J.*, 1953, **55**, 371) to 3β-hydroxyandrostane-12 : 17-dione (VI), which formed a monoacetate and was oxidised by *N*-bromoacetamide in aqueous acetone to androstane-3 : 12 : 17-trione. *Inter alia* we observed that (II; R = R″ = H, R′ = O) with one molar proportion of bromine gives a monobromo-derivative, which regenerates the original ketone on successive treatment with sodium iodide and potassium acetate in acetone.

Reaction of 17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (IV; R = O) with excess of ethylene glycol and boron trifluoride–ether complex led to the formation of the 3 : 12-diethylene ketal (IV; R = ·O·CH_2·CH_2·O·), which reverted to the original diketone on treatment with 90% acetic acid. The constitution assigned to the ketal was confirmed by its reduction with sodium borohydride to 3 : 3-12 : 12-bisethylenedioxy*allo*pregnane-17α : 20ξ-diol (V; R = ·O·CH_2·CH_2·O·), hydrolysed by 90% acetic acid to 17α : 20ξ-dihydroxy*allo*-pregnane-3 : 12-dione (V; R = O) which formed a 20-monoacetate and was separately obtained by oxidation of (II; R = R″ = H, R′ = O) with *N*-bromoacetamide.



The foregoing results reveal that in 17α-hydroxy*allo*pregnane-12 : 20-diones ketal formation occurs exclusively on the 12-carbonyl group. In accordance therewith we find that 3β-acetoxy*allo*pregnane-12 : 20-dione (cf. Part II) forms only a monoethylene ketal and monohemithioethylene ketal which are accordingly formulated as 12-derivatives.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube.

12 : 12-*Ethylenedioxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (I; R = H, R′ = ·O·CH_2·CH_2·O·).—3β : 17α-Dihydroxy*allo*pregnane-12 : 20-dione (8·75 g.) in ethylene glycol (90 ml.) was treated with boron trifluoride–ether complex (14 ml.). After 16 hr. at room temperature the solution was diluted with chloroform and washed neutral with water. After removal of the solvent, the residue was purified from chloroform–ethyl acetate or from methanol. The 12-*ethylene ketal* formed crystals, m. p. 255—259° (softens 252°), $[\alpha]_D^{26}$ +74° (*c*, 0·422) (Found : C, 70·2; H, 9·4. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%). The *acetate* formed prisms, m. p. 209—211°, $[\alpha]_D^{25}$ +68° (*c*, 0·434), from methanol or acetone–hexane (Found : C, 69·3; H, 8·5. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

12 : 12-*Ethylenedioxy*allo*pregnane*-3β : 17α : 20ξ-*triol* (II; R = R″ = H, R′ = ·O·CH_2·CH_2·O·).—The foregoing ketal (2 g.) in methanol (240 ml.) was treated portionwise with sodium borohydride (2 g.) in water (20 ml.). Acetic acid (3 ml.) was added after 3 hr., the solvent removed under reduced pressure, and the residue crystallised from acetone–methanol. The *triol* formed prisms, m. p. 223—225°, $[\alpha]_D^{25}$ +22° (*c*, 0·468) (Found : C, 70·3; H, 9·8. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%).

3β : 17α : 20ξ-*Trihydroxy*allo*pregnan*-12-*one* (II; R = R″ = H, R′ = O).—The foregoing compound (400 mg.) was heated with 90% acetic acid (12 ml.) for 45 min. on the steam-bath. The product was isolated with chloroform and purified from acetone. 3β : 17α : 20ξ-*Trihydroxy*-allo*pregnan*-12-*one* formed prisms, m. p. 222—224°, $[\alpha]_D^{25}$ +54° (*c*, 0·480) (Found: C, 71·4; H, 10·0. $C_{21}H_{34}O_4$ requires C, 71·9; H, 9·7%). The 3 : 20-*diacetate* formed needles, m. p. 149—150°, $[\alpha]_D^{27}$ +56° (*c*, 0·460) (Found: C, 69·1; H, 8·4. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·7%).

3β-*Hydroxy*-17α : 20-iso*propylidenedioxy*allo*pregnane*-12 : 20-*dione* (III; R = H).—3β : 17α : 20ξ-Trihydroxy*allo*pregnane-12 : 20-dione (200 mg.) in acetone (20 ml.) was treated with toluene-*p*-sulphonic acid (50 mg.) for 20 hr. at room temperature. After extraction with ether the *product* was purified from ether–hexane. It had m. p. 161—163°, $[\alpha]_D^{24}$ +31° (*c*, 0·400) (Found: C, 73·8; H, 9·7. $C_{24}H_{38}O_4$ requires C, 73·5; H, 9·8%). The *acetate* formed plates, m. p. 188—190°, $[\alpha]_D^{25}$ +24° (*c*, 0·414) (Found: C, 72·7; H, 9·3. $C_{26}H_{40}O_5$ requires C, 72·2; H, 9·3%).

3β-*Hydroxyandrostane*-12 : 17-*dione* (VI).—3β : 17α : 20ξ-Trihydroxy*allo*pregnan-12-one (1·47 g.) in 50% acetic acid (150 ml.) was shaken with sodium bismuthate (24 g.) for 9 hr., after which the mixture was poured into potassium hydroxide solution (15 g. in 1 l.) and extracted with benzene (200 ml.). The product so obtained proved difficult to purify. Acetylation gave 3β-*acetoxyandrostane*-12 : 17-*dione*, glistening plates, m. p. 165—166°, $[\alpha]_D^{19}$ +164° (*c*, 0·25) (Found: C, 72·9; H, 8·4. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), after crystallisation from acetone–hexane. Hydrolysis with potassium carbonate in aqueous methanol furnished 3β-*hydroxyandrostane*-12 : 17-*dione*, silky needles, m. p. 127—129°, $[\alpha]_D^{19\cdot5}$ +173° (*c*, 0·25) (Found: C, 75·2; H, 9·8. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%).

Androstane-3 : 12 : 17-*trione*.—The foregoing compound (600 mg.) was treated with *N*-bromoacetamide (600 mg.) in aqueous acetone (150 ml. of 90%) for 8 hr. at room temperature. The mixture was poured into water and the product isolated with chloroform and debrominated with zinc dust in acetic acid (20 ml. at 60° for 30 min.). Crystallisation from acetone–hexane yielded *androstane*-3 : 12 : 17-*trione*, crystals, m. p. 179—181°, $[\alpha]_D^{19\cdot5}$ +227° (*c*, 0·25) (Found: C, 75·2; H, 8·9. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7%).

11ξ-*Bromo*-3β : 17α : 20ξ-*trihydroxy*allo*pregnan*-12-*one*.—A stirred solution of 3β : 17α : 20ξ-trihydroxy*allo*pregnan-12-one (1·2 g.) in chloroform (20 ml.) was treated dropwise with bromine (27 ml.; 0·128M in chloroform). The product, after crystallisation from chloroform–ether, yielded the 11ξ-*bromo*-derivative, m. p. 158—159°, $[\alpha]_D^{24}$ −42° (*c*, 0·40) (Found: C, 59·4; H, 7·7; Br, 20·3. $C_{21}H_{33}O_4Br$ requires C, 58·7; H, 7·7; Br, 18·7%).

3 : 3-12 : 12-*Bisethylenedioxy*-17α-*hydroxy*allo*pregnane*-20-*one*.—A solution of (IV; R = O) (2 g.) in benzene (80 ml.) and ethylene glycol (20 ml.) was distilled slowly to remove traces of water. Toluene-*p*-sulphonic acid (75 mg.) was then added and the solution heated under reflux for 6 hr. The product, after crystallisation from ethyl acetate, yielded the *diketal*, m. p. 222—224°, $[\alpha]_D^{25}$ +80° (*c*, 0·450) (Found: C, 69·2; H, 8·7. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%), also prepared by the boron trifluoride route (see above).

3 : 3-12 : 12-*Bisethylenedioxy*allo*pregnane*-17α : 20ξ-*diol*.—This *diketal*, prepared by reduction of the foregoing compound with sodium borohydride in aqueous methanol, formed hexagonal prisms, m. p. 211—213°, $[\alpha]_D^{27}$ +25° (*c*, 0·398) (Found: C, 68·7; H, 9·1. $C_{25}H_{40}O_6$ requires C, 68·8; H, 9·2%).

17α : 20ξ-*Dihydroxy*allo*pregnane*-3 : 12-*dione* (V; R = O).—(i) The foregoing diketal was hydrolysed with 90% acetic acid for 1 hr. at 100° and the product crystallised from aqueous methanol. 17α : 20ξ-*Dihydroxy*allo*pregnane*-3 : 12-*dione* formed glistening leaflets, m. p. 227—229° (decomp.), $[\alpha]_D^{22}$ +75° (*c*, 0·472) (Found: C, 72·4; H, 9·1. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%).

(ii) 3β : 17α : 20ξ-Trihydroxy*allo*pregnan-12-one (250 mg.) in *tert.*-butanol (7 ml.) and water (0·5 ml.) was treated with *N*-bromoacetamide (250 mg.) for 7 hr. at room temperature. The product, after brief debromination with zinc dust in acetic acid, was crystallised from acetone–hexane, to give the product described under (i), m. p. and mixed m. p. 231—233°, $[\alpha]_D^{24}$ +86° (*c*, 0·446).

Acetylation of the compounds from (i) and (ii) gave 20-*acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12-*dione*, m. p. 205—206°, $[\alpha]_D^{28}$ +79° (*c*, 0·418) (Found: C, 70·8; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·8%), after crystallisation from ether–hexane.

3β-*Acetoxy*-12 : 12-*ethylenedioxy*allo*pregnan*-20-*one* had m. p. 155—157°, $[\alpha]_D^{25}$ +99° (*c*, 0·418) (Found: C, 72·5; H, 8·9. $C_{25}H_{38}O_5$ requires C, 71·8; H, 9·1%), after crystallisation from ether–hexane and finally from methanol.

The 3β-*hydroxy*-20-*ketone*, prepared by hydrolysis of the foregoing compound (1·72 g.) in

methanol (150 ml.) with potassium carbonate (1·0 g.) in water (10 ml.) for 1 hr. under reflux, had m. p. 195—197°, $[\alpha]_D^{24}$ +97° (Found: C, 73·0; H, 9·5. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%), after purification from chloroform–ether.

3β-*Acetoxyallopregnane*-12 : 20-*dione* 12-*hemithioethylene ketal*, m. p. 175—177°, $[\alpha]_D^{24}$ +112° (*c*, 0·528) (Found: C, 68·7; H, 8·4; S, 7·5. $C_{25}H_{38}O_4S$ requires C, 69·1; H, 8·8; S, 7·4%), was obtained by treating 3β-acetoxy*allo*pregnane-12 : 20-dione (1 g.) in freshly distilled dioxan (7·5 ml.) with 2-mercaptoethanol (2 ml.), fused zinc chloride (1·5 g.), and anhydrous sodium sulphate (1·5 g.) for 18 hr. at room temperature. The product in benzene–light petroleum (1 : 1) was run through an alumina column (150 g.), eluted with the same solvent mixture (150 ml.), and crystallised from chloroform–ether.

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, March 9th*, 1954.]

Reactions of Diphenyl Phosphates of Δ^5-Sterols.

By J. H. TURNBULL and WALTER WILSON.

[Reprint Order No. 4749.]

Crystalline diphenyl phosphates are made from several sterols and diphenyl phosphorochloridate in pyridine. The solvolytic reactions of Δ^5-steryl diphenyl phosphates are interesting; thus cholesteryl diphenyl phosphate is hydrolysed by alkali to phenol and cholesteryl dihydrogen phosphate. An alternative mode of fission occurs with hydrogen chloride (or bromide) in warm acetic acid, and diphenyl hydrogen phosphate and 3β-chloro(bromo)cholest-5-ene are formed. 3β-Halogeno-Δ^5-steroids are obtained in high yields by these reactions, in which the configuration at $C_{(3)}$ is retained. Cholesteryl dihydrogen phosphate is associated, usually dimeric, and has been mistaken for *sym.*-dicholesteryl dihydrogen pyrophosphate.

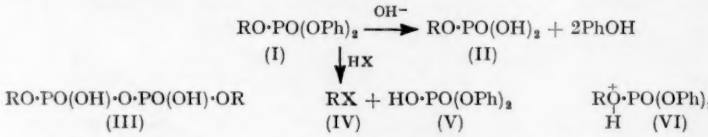
DIRECT phosphorylation of sterols is not very satisfactory for preparative purposes (von Euler and Bernton, *Ber.*, 1927, **60**, 1720; von Euler, Wolf, and Hellström, *Ber.*, 1929, **62**, 2451; Plimmer and Burch, *J.*, 1929, 279, 292; Wagner-Jauregg, Lennartz, and Kothny, *Ber.*, 1941, **74**, 1513; Reichstein and Schindler, *Helv. Chim. Acta*, 1940, **23**, 669; Müller, Langerbeck, and Riedel, *Z. physiol. Chem.*, 1944, **281**, 29). Indirect phosphorylation using phosphoramidic chlorides has not been fully investigated; it has been used for the preparation of dicholesteryl hydrogen phosphate (Zeile and Kruckenberg, *Ber.*, 1942, **75**, 1127; cf. Zetsche and Buttiker, *Ber.*, 1940, **73**, 47). Phosphates have been made recently from steroid hormones, by using tetrabenzyl pyrophosphate (Roche Products, Atherton, and Todd, B.P., 674,087; *Chem. Abs.*, 1953, **47**, 6436).

We have obtained crystalline diphenyl phosphates from several sterols and diphenyl phosphorochloridate in pyridine (see Table). The solvolytic reactions of these products have been studied, one objective being a route to steryl phosphates.

Alkaline hydrolysis of cholesteryl diphenyl phosphate (I; R = cholesteryl) afforded phenol (2 equivs.) and cholesteryl dihydrogen phosphate (II), m. p. 162—163°. The absence of free cholesterol in the hydrolysate confirms the alkali-stability of alkyl hydrogen phosphates (*e.g.*, Kosolapoff, "Organophosphorus Compounds," Wiley, New York, 1950, p. 233; Davis and Ross, *J.*, 1952, 4299). The recorded m. p. of cholesteryl dihydrogen phosphate varies considerably; von Euler *et al.* (*locc. cit.*) give m. p. 195—196° and 193°, and Wagner-Jauregg *et al.* (*loc. cit.*), using von Euler's preparative method, obtained a product of m. p. 175°. The molecular weight of cholesteryl dihydrogen phosphate as usually determined is about twice the theoretical value. This association, also observed with dicholesteryl hydrogen phosphate (Zeile and Kruckenberg, *loc. cit.*), has led to the erroneous pyrophosphate formulation (III; R = cholesteryl) (Wagner-Jauregg *et al.*, *loc. cit.*), which appeared to be confirmed by the isolation of "half" sodium or potassium

salts (Wagner-Jauregg and Lennartz, *Ber.*, 1942, **75**, 178). However, alkyl dihydrogen phosphates commonly form "half" salts (*i.e.*, salts containing one atom of sodium for two molecules of acid) (Friedman and Seligman, *J. Amer. Chem. Soc.*, 1951, **73**, 5292; Wagner-Jauregg and Wildermuth, *Ber.*, 1944, **77**, 481). The electrometric titration of cholesteryl dihydrogen phosphate was difficult because of the solubilities of the substance and its salts. In methanol–benzene, only one acidic hydrogen was revealed, and this result does not therefore exclude the pyrophosphate structure (III). It is unlikely, however, that a pyrophosphate could have been formed or would have survived the strongly alkaline hydrolysis; also, our product has no well-defined infra-red absorption in the 930—950 cm.$^{-1}$ region, where the pyrophosphate P–O–P group often absorbs (cf. Bergmann, Littauer, and Pinchas, *J.*, 1952, 847).

An alternative mode of fission of cholesteryl diphenyl phosphate occurs with hydrogen chloride in warm acetic acid, and 3β-chlorocholestene (IV; R = cholesteryl, X = Cl) and diphenyl hydrogen phosphate (V) were isolated. The diphenyl phosphates of stigmasterol and dehydro*epi*androsterone, which are also Δ^5-compounds, behaved in the same way; similarly, hydrogen bromide yielded the corresponding 3β-bromo-compounds. The 3-halides were obtained in high yields, with retention of configuration at $C_{(3)}$. The solvent appears to play a critical rôle in these reactions, which did not occur when the acetic acid was replaced by dioxan. The reaction is probably facilitated by the tendency of the 3-substituent to separate as a stable diphenyl phosphate anion. Initial activation by formation of an oxonium salt (*e.g.*, VI) with protons may be necessary before dealkylation



can occur (cf. Shoppee and Summers, *J.*, 1952, 3361); in dioxan, the solvent may be sufficiently basic to inhibit oxonium salt formation from steryl diphenyl phosphates. The tendency of alkyl phosphates to undergo ionic alkyl–oxygen fission is indicated, for example, by experiments on their dealkylation by hydrogen halides (Gerrard, Green, and Nutkins, *J.*, 1952, 4076; Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611), and by the reaction between benzyl phosphates and lithium chloride or tertiary amines (Clark and Todd, *J.*, 1950, 2030). Also, ionic elimination reactions occur in phosphates of β-hydroxycarbonyl compound (Linstead, Owen, and Webb, *J.*, 1953, 1211; Brown, Fried, and Todd, *Chem. and Ind.*, 1953, 352; Riley, Turnbull, and Wilson, *ibid.*, p. 1181).

The reaction of optically active alkyl phosphates with hydrogen halides normally gives alkyl halides with *inversion* of configuration (Gerrard, Green, and Nutkins, *loc. cit.*; Bevan, Brown, Gregory, and Malkin, *J.*, 1953, 127). The retention of configuration observed with the Δ^5-sterol derivatives is apparently anomalous. However, similar occurrences have been satisfactorily accounted for by Shoppee and his co-workers (*J.*, 1952, 3361 and earlier papers; cf. Landauer and Rydon, *J.*, 1953, 2224). There is convincing evidence that the 5 : 6-double bond in steroids can participate in reactions at $C_{(3)}$; as a result, either substitution with retention of configuration at $C_{(3)}$, or rearrangement to 6β-substituted *cyclo*steroids, occurs. In our experiments, *cyclo*steroids were not detected; they would have been rapidly converted under the conditions used into 3β-halogeno-Δ^5-steroids (cf. Shoppee and Summers, *loc. cit.*).

Experimental

$[\alpha]_D$ were measured in chloroform.

Cholesteryl Diphenyl Phosphate.—Dry cholesterol (2·5 g.) was dissolved in dry pyridine (25 c.c.) and diphenyl phosphorochloridate (2·0 g.) added at 0°. After 16 hr. at 45°, excess of ice was added. The crystals which soon separated were recrystallised from ethanol; for yield, etc., see Table. The procedures for making all the *diphenyl phosphates* were similar.

Alkaline Hydrolysis of Cholesteryl Diphenyl Phosphate.—The diphenyl phosphate (600 mg.), ethanol (30 c.c.), and 4N-potassium hydroxide (8 c.c.) were heated at 95° for 19 hr. The solution

was cooled, diluted with 60% ethanol, and filtered through Amberlite resin IR-120. The percolate was strongly acid and formed a gel when kept. Solvent was removed at 40° in a vacuum, and the solid residue (360 mg.) was crystallised from benzene–light petroleum (b. p. 40—60°), then from ethyl acetate, affording cholesteryl dihydrogen phosphate, white needles, m. p. 162—163°, $[\alpha]_D$ −30°, $\lambda_{max.}$ 263 (ε 1150) [Found: C, 71·0; H, 10·3%; *M* (ebullioscopic; benzene), 874; *M* (Rast), 720. Calc. for $C_{27}H_{47}O_4P$: C, 70·85; H, 10·15%; *M*, 467]. Electrometric titration (glass electrode) of a benzene solution with methanolic potassium hydroxide gave an equivalent weight of 507 (calc. for one acidic hydrogen, 467). In a further experiment, cholesteryl diphenyl phosphate (100 mg.) was similarly treated with alkali, and the ethanol removed. The residue consumed 40·0 c.c. of 0·042N-bromine water, corresponding to the presence of 1·75 mols. of phenol (also, the 2 : 4 : 6-tribromophenol formed was isolated). The phosphate was precipitated, less pure, by acidification of alkaline hydrolysates.

Reaction of Cholesteryl Diphenyl Phosphate with Hydrogen Chloride.—The diphenyl phosphate (200 mg.), acetic acid (2 c.c.), and concentrated hydrochloric acid (0·2 c.c.) were warmed (60°) for 20 min. The clear solution soon deposited an oil which crystallised on cooling. The product (150 mg.; m. p. 67—70°) recrystallised from glacial acetic acid, and gave 3β-chlorocholest-5-ene (85 mg.) as glistening plates, m. p. 92—93°, $[\alpha]_D^{20}$ −26·4° (Found: C, 79·8; H, 11·25. Calc. for $C_{27}H_{45}Cl$: C, 80·05; H, 11·1%). Beynon, Heilbron, and Spring (*J.*, 1936, 909) give m. p. 95°, $[\alpha]_D$ −27·4°. The aqueous liquors, after separation of the crude product, were evaporated to dryness and treated with aqueous *cyclo*hexylamine, affording colourless needles of *cyclo*hexylammonium diphenyl phosphate (25 mg.), m. p. 197—199° (Found: N, 4·25. Calc. for $C_{12}H_{11}O_4P,C_6H_{13}N$: N, 4·0%) (Corby, Kenner, and Todd, *J.*, 1952, 1241, give m. p. 198—199°).

Sterol	Diphenyl phosphate	
Cholesterol	Plates from methanol	M. p. 114—116°, $[\alpha]_D$ −9·2°, $\lambda_{max.}$ 261·5 (ε 660) (Found: C, 75·5; H, 9·0; P, 5·0. $C_{39}H_{55}O_4P$ requires C, 75·7; H, 9·0; P, 5·0%).
Stigmasterol	Needles from methanol	M. p. 99—101°, $[\alpha]_D$ −22°, $\lambda_{max.}$ 261·5 (ε 706) (Found: C, 76·5; H, 8·6. $C_{41}H_{57}O_4P$ requires C, 76·4; H, 8·9%).
Fucosterol	Needles from methanol	M. p. 80—81°, $[\alpha]_D$ −24°, $\lambda_{max.}$ 261·5 (ε 671) (Found: C, 76·7; H, 8·8. $C_{41}H_{57}O_4P$ requires C, 76·4; H, 8·9%).
Dehydro*epi*androsterone	Chromatographed,[1] needles from light petroleum (b. p. 60—80°)	M. p. 94—96° (Found: C, 71·1; H, 7·4. $C_{31}H_{37}O_5P$ requires C, 71·5; H, 7·2%).
5-Dihydroergosterol	Cryst. from methanol	M. p. 74—76°, $[\alpha]_D$ −12° (Found: C, 76·0; H, 8·7. $C_{40}H_{55}O_4P$ requires C, 76·2; H, 8·8%).
Zymosterol	Chromatographed,[2] colourless gum	Found: C, 75·6; H, 8·6. $C_{39}H_{53}O_4P$ requires C, 75·9; H, 8·7%.
Ergosterol	Cryst. from methanol	M. p. 106—107°, $[\alpha]_D$ −49° (Found: C, 76·7; H, 8·6. $C_{40}H_{53}O_4P$ requires C, 76·4; H, 8·5%).
7-Dehydrocholesterol	Small rosettes, chromatographed,[3] cryst. from methanol	M. p. 75—77°, $[\alpha]_D$ −31° (Found: C, 75·6; H, 8·6; $C_{39}H_{53}O_4P$ requires C, 75·9; H, 8·7%).
Dehydroergosterol	Chromatographed,[4] needles from methanol	M. p. 82—84° (Found: C, 76·3; H, 8·15. $C_{40}H_{51}O_4P$ requires C, 76·6; H, 8·2%).
Calciferol	Chromatographed, colourless gum (unstable)	Found: C, 75·0; H, 8·9. $C_{40}H_{59}O_4P$ requires C, 76·4; H, 8·5%. $\lambda_{max.}$ 264 (ε 15,150). Calciferol has $\lambda_{max.}$ 265 (ε 19,150).

[1] Eluted with 1 : 1 benzene–light petroleum. [2] Eluted with 2 : 3 benzene–light petroleum. [3] Eluted with 1 : 1 benzene–light petroleum. [4] Eluted with 1 : 1 benzene–light petroleum. Unstable.

3β-*Bromocholest-5-ene.*—Cholesteryl diphenyl phosphate (100 mg.) was warmed (60°) with glacial acetic acid and 48% aqueous hydrobromic acid. The product (70 mg.; m. p. 85—93°) formed glistening plates, m. p. 97—98°, $[\alpha]_D$ −18°, from acetic acid (Found: C, 72·6; H, 10·0. Calc. for $C_{27}H_{45}Br$: C, 72·2; H, 10·0%) (Beynon, Heilbron, and Spring, *loc. cit.*, give m. p. 98° $[\alpha]_D$ −20·8°).

3β-*Chlorostigmast-5-ene.*—Diphenyl stigmasteryl phosphate (70 mg.) and hydrochloric–acetic acid similarly afforded a product (40 mg.; m. p. 83—86°), which crystallised from ethanol as plates, m. p. 89—90° (Found: C, 80·8; H, 10·8. Calc. for $C_{29}H_{47}Cl$: C, 80·8; H, 11·0%) (Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711, give m. p. 83°).

3β-*Chloroandrost-5-en-17-one.*—The crude product (50 mg.; m. p. 128—140°) from dehydro-

*epi*anhydrosterone diphenyl phosphate (100 mg.) and hydrochloric–acetic acid crystallised from methanol, giving colourless plates, m. p. 155—157°, $[\alpha]_D$ +7·7° (Found: C, 73·65; H, 9·1. Calc. for $C_{19}H_{27}OCl$: C, 74·3; H, 8·9%) (Wallis and Fernholz, *J. Amer. Chem. Soc.*, 1937, **59**, 764, give m. p. 154°, $[\alpha]_D$ +14·6°; Butenandt and Grosse, *Ber.*, 1936, **69**, 2776, m. p. 155—157°, $[\alpha]_D$ +14°).

The authors are grateful to Professor M. Stacey, F.R.S., for guidance and to Dr. C. L. Hewett of Organon Laboratories Ltd. for a gift of dehydro*epi*androsterone.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15. [*Received, October 24th*, 1953.

The Heats of Formation of Complex Ions containing Ethylenediamine.

By T. DAVIES, (MISS) S. S. SINGER, and L. A. K. STAVELEY.

[Reprint Order No. 5090.]

A calorimeter is described for the accurate measurement of the heats of reactions which take place rapidly in solution, and of heats of solution, neutralisation, and dilution. Its capabilities have been tested by measurement of the heat of neutralisation of sodium hydroxide by hydrochloric acid and of the heat of solution of potassium chloride. In favourable circumstances an accuracy of 0·1% is possible. The calorimeter has been used to measure the two heats of neutralisation of ethylenediamine, and the heats of formation of complex ions of ethylenediamine and copper, nickel, cadmium, and zinc. By carrying out experiments with varying proportions of metal and amine, heats of formation have been obtained for the ions $M(en)_2^{++}$ and (except for copper) for the ions $M(en)_3^{++}$. These heats of formation have been combined with the known free-energy changes to evaluate the entropies of formation of the ions. The results are discussed, with special reference to the significance of the entropy change in complex-ion formation of this kind.

IN recent years, increasing interest has been shown in the physical chemistry of complex-ion formation. In particular, numerous measurements have been made of the stability constants of complex ions and hence of their free energies of formation. If their heats of formation are also known the corresponding entropy change can, of course, be evaluated. Usually, however, either these heats of formation have not yet been determined, or else the only values available are those calculated from stability-constant measurements at more than one temperature. The reliability of such values often seems to be questionable, primarily because the range of temperatures over which the measurements were made has almost always been too small. It is undoubtedly better to measure the heats of formation calorimetrically, preferably under more or less the same conditions of concentration and ionic strength as those used in the measurement of the stability constants.

Some direct determinations of the heats of formation of metal–ammonia complex ions in solution have recently been carried out by Fyfe (*J.*, 1952, 2023), with an accuracy of $\sim\pm3\%$. These determinations were made upon rather concentrated solutions (~1M). We now describe a calorimeter for the measurement of heats of complex-ion formation with which a greater precision can be obtained while using more dilute solutions, so that the results can be combined with measurements of stability constants made in this laboratory by H. M. N. H. Irving and his co-workers (and by others elsewhere), using solutions of the same order of dilution. The accuracy of the calorimeter has been carefully tested by measuring (*a*) the heat of solution of potassium chloride in water and (*b*) the heat of neutralisation of sodium hydroxide by hydrochloric acid (which are processes involving accurately known heat-content changes), and in favourable circumstances the calorimeter is capable of a precision of $\pm0\cdot1\%$. The calorimeter has been used to determine the heats of formation of complex ions formed from ethylenediamine and nickel, cupric, zinc, and cadmium ions. Since, in general, any one metal forms more than one complex ion with ethylenediamine, it is necessary to know the successive stability constants for each system,

and also to carry out measurements using different proportions of the metal and the diamine, in order to evaluate the heats of formation of the several complex ions. Inaccuracy in the values of the stability constants, therefore, has an effect on the values derived for the corresponding heat-content changes and, for some at least of the systems we have studied, the uncertainty in the stability constants is such that the values ultimately derived for the entropy changes may be wrong by several entropy units. We shall therefore present our thermochemical data in a way which will permit heats of formation to be recalculated from them with other values of the stability constants than those selected by us.

Finally, we report the results of measurements of the first and the second heat of neutralisation of ethylenediamine. These were carried out because of the discrepancy between the published values obtained indirectly from dissociation-constant measurements. The existence of this discrepancy means that not only must some of the values reported for these dissociation constants be wrong, but also stability constants estimated by methods which require a knowledge of these dissociation constants.

Experimental

In its main features, the calorimeter is similar to that described by Pitzer (*J. Amer. Chem. Soc.*, 1937, **59**, 2365), but differs from his in not having an evacuated ground-glass stopper and in the arrangements made for introducing the solution or component present in smaller amount. Its construction is shown in the figure. The top of the Dewar vessel **1**, which held about 1 l., was closed with a brass cap **2** resembling a top hat. This was about 3 in. high so as to increase the length of the tubes passing through a central hole in its roof into the liquid in the calorimeter, thereby reducing the thermal gradient along these tubes. The flange on the brass cap was held by four screw clips **3** to a flange on the top of the Dewar vessel, the joint being made water-tight with a little Vaseline.

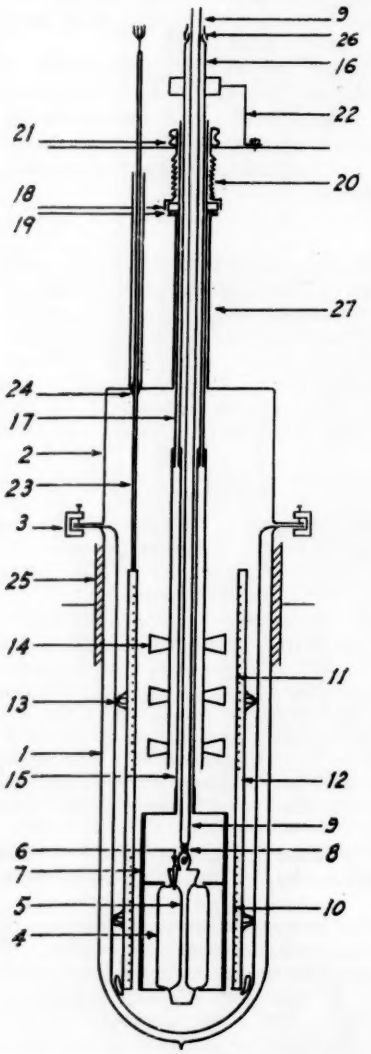
The component present in smaller amount was contained in a bottle **4** with ground-glass stoppers at top and bottom, which were sealed to a glass rod **5**. The bottle was filled through a small hole in the upper stopper (later closed by a ground-glass plug **6**). When in place in the calorimeter, the bottle fitted loosely in a gold-plated metal frame **7**. A loop of platinum wire was attached to the upper stopper and also to the hook **8** on the bottom of the central glass tube **9**. When the upper end of this glass tube was pulled, the bottle therefore opened at both ends and its contents were quickly swept out by the current of liquid moving upwards round the bottle. There was no detectable "heat of opening." The stirrer was rotated throughout the whole experiment at a constant speed of 160 rev./min., so that (as is customary in calorimetry of this kind) it was assumed in the evaluation of the temperature change caused by the reaction or by electrical heating that the rate of generation of the heat of stirring (which in fact was very small) was constant. It must be clearly understood that the only moving part of the calorimetric assembly is the stirrer **14** and the shaft **17** bearing it. The framework **7** holding the bottle **4** is fixed, since the glass tube **15** supporting the framework is cemented to the brass tube **16**, which is firmly held by the clamp **22**. The tube **17** therefore rotates between the two fixed tubes **27** and **16**.

The heater **10** and resistance thermometer **11** were contained within two sealed concentric copper cylinders **12** which were gold-plated on the outside, and kept central by rubber-protected projections **13**.

Energy input was determined by using a potentiometer to measure the current through the manganin heater and a Venner electrically-operated stop-watch to measure (to 0·02 sec.) the time of passage of the current. Changes in the resistance of the copper resistance thermometer were measured by using the circuit described by Pitzer. All resistances were kept in a thermostat. Temperature changes of $5 \times 10^{-5}°$ could be detected. The actual temperature changes were $\sim 1°$ in the heat of solution experiments, $\sim 0{\cdot}3°$ in the heat of neutralisation experiments, and between 0·05 and 0·25° in the experiments on complex ions.

In the experiments on complex-ion formation, a solution of ethylenediamine in 0·1M-potassium chloride was placed in the double-stoppered bottle **4**, the weight of the solution being found from the increase in the weight of the bottle. (In experiments in which ethylenediamine or sodium hydroxide was used, great care was taken to exclude atmospheric carbon dioxide from all solutions.) A fixed volume (~ 1 l.) of 0·1M-potassium chloride was siphoned into the Dewar vessel **1**, and a known amount of a concentrated solution of the metallic sulphate (also in 0·1M-potassium chloride) was added to it from a weight pipette. The calorimeter was then assembled outside the thermostat, transferred to the thermostat (which was maintained at 25·00° $\pm$ 0·005°),

and the contents of the calorimeter were heated electrically until they were at a suitable temperature below 25°. Never in a run did the temperature within the calorimeter exceed 25°. The experiment was then carried out with fore and after periods of at least 10 min.; mixing seemed to be complete within 10 sec. of opening the bottle, since after this period, linear time–temperature relationship was re-established. The calorimeter was then cooled to about the same tem-



1, Silvered Dewar vessel.
2, Brass cap with plane flange.
3, Screw clips.
4, Bottle, capacity ~25 c.c.
5, Glass rod, sealed to both stoppers.
6, Filling hole and plug.
7, Gold-plated frame with detachable base, and shelf to restrict upward movement of bottle.
8, Glass hook.
9, Central glass tube.
10, Heater of 32 s.w.g. manganin, resistance ~100 ohms, with leads of 24 s.w.g. copper.
11, Copper resistance thermometer, 42 s.w.g., resistance ~96 ohms at 25°, with 23 s.w.g. manganin leads.
12, Hollow gold-plated copper cylinder.
13, Rubber-protected projections to centre cylinder.
14, Glass stirrer, sending liquid up the inside of the gold-plated cylinder.
15, Glass tube cemented to the frame 7.
16, Brass tube cemented at lower end to glass tube 15.
17, Brass tube cemented at lower end to glass stirrer 14.
18, Detachable collar.
19, Greased leather washer.
20, Flexible drive fixed to collar 18 by grub screws.
21, Pulley.
22, Clamp to hold tube 16 rigid.
23, Thin-walled brass conduit for leads.
24, Rubber seal.
25, Detachable brass clamp for support of calorimeter.
26, Rubber sleeve.
27, Brass tube soldered to brass cap 2.

The possibility of evaporation from inside the calorimeter was prevented by the washer 19 and the rubber seals 24 and 26, and by making the central brass tubes (which were greased) as close a fit as possible.

The level of liquid in the Dewar vessel was about 1 cm. above the top of the cylinder 12, and that of the water in the thermostat about 5 cm. above the top of the cap 2.

perature as before the bottle was opened; this was conveniently done by dropping powdered solid carbon dioxide down the central glass tube 9, and the "electrical energy equivalent" experiment was carried out. Usually three determinations of the "electrical energy equivalent" were made. The heat generated in the chemical experiment was then calculated by standard methods (see, *e.g.*, Sturtevant in Weissberger, "Technique of Organic Chemistry," Interscience Publ., 1949, Vol. I, Physical Methods, Part I, p. 731). It was found by experiment that the heat of dilution of ethylenediamine under the conditions of the experiments was negligible.

The metallic salt solutions were made up from "AnalaR" samples, and their concentrations

determined by standard gravimetic methods. Ethylenediamine was dried over potassium hydroxide pellets and then twice fractionated.

In the heat of neutralisation experiments a known amount of hydrochloric acid (which had been standardised gravimetrically by silver chloride precipitation) was placed in the bottle, and about 1 l. of dilute carbon dioxide-free sodium hydroxide solution (representing a slight excess) in the Dewar vessel. In the measurements of the heat of solution of potassium chloride, the salt required about 10 min. to dissolve completely, and the fore and after periods were accordingly prolonged. The thermal exchange corrections were therefore larger here than for the more rapid reactions, and consequently the precision of the heat of solution measurements is not quite as high as that of the heat of neutralisation measurements.

Results.—The unit in which all results are expressed is the thermochemical calorie (=4·1833 international joules, =4·1840 absolute joules).

Results on the heat of solution of potassium chloride are presented in Table 1. Since the concentration of the solution produced varied slightly from one experiment to another, small corrections have been applied to give values at an arbitrarily fixed dilution of 1 mole of salt to 167 moles of water. Two reviews of previous determinations of the heat of solution of this salt have recently been published, one by Miščenko and Yu. Ya. Kaganovich (*J. Appl. Chem., U.S.S.R.*, 1949, **22**, 1078; *Chem. Abs.*, 1950, **44**, 921), and the other by Rossini ("Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards, Washington, 1952). The values given by these authors, corrected to our dilution, are included for comparison in Table 1.

TABLE 1. *Heat of solution of potassium chloride at 25°.*

x = Moles of water per mole of salt; ΔH = heat absorbed (in cal./mole) at this dilution; $\Delta H_{corr.}$ = heat of solution corrected to $x = 167$.

x	166·7	165·7	166·6	175·4	167·1
ΔH	4193	4195	4174	4183	4179
$\Delta H_{corr.}$	4193	4196	4174	4180	4179

Mean = 4184 ± 8

Miščenko and Yu. Ya. Kaganovich give 4187; Rossini gives 4194.

Four measurements of the heat of neutralisation of sodium hydroxide by hydrochloric acid were made, exactly the same concentrations being used throughout, that of the alkali being about N/30. After correction to infinite dilution, using for this purpose the same data as Pitzer (*loc. cit.*), the individual values were: −13,345, −13,355, −13,378, −13,344 cal./mole. The mean is −13,356 ± 12. The value derived from a critical examination of other data (Rossini, *Bur. Stand. J. Res.*, 1931, **6**, 855), when converted to 25° by Pitzer, was −13,352 cal./mole. Pitzer himself recorded a measured value of −13,363 ± 16 cal./mole.

TABLE 2. *Heat of mixing of hydrochloric acid and ethylenediamine.*

A = Moles of hydrochloric acid × 10^3; B = moles of ethylenediamine × 10^3; Q = heat evolved (in cal.).

A	24·48	24·36	24·19	9·865	9·863	9·890	9·884	9·800	9·796
B	9·637	9·618	9·620	11·51	11·56	11·57	11·58	11·49	11·52
Q	219·7	220·0	220·2	116·0	116·2	118·5	119·0	116·0	117·5

In Table 2 we present the results for the heat evolved on mixing of solutions of ethylenediamine and hydrochloric acid of different concentrations. From these results, values of ΔH_1 and ΔH_2 have been calculated, these being the heat content changes in the processes $(en)H^+ \rightleftharpoons (en) + H^+$, $(en)H_2^{++} \rightleftharpoons (en)H^+ + H^+$, respectively, in aqueous solution at 25° in 0·1M-potassium chloride. In these experiments, the constituent present in excess furnished the more dilute solution before mixing. In the first three experiments, the acid was in such excess that the doubly charged cation was virtually completely formed. The mean value for $(\Delta H_1 + \Delta H_2)$ per g.-ion is 22,850 ± 40 cal. In the remaining experiments, about 99% of the amine was converted into the singly charged ion, and the remainder into the doubly charged ion. To allow for the latter, the amounts of the two ions were calculated by using the dissociation constants at 25° given by Everett and Pinsent (*Proc. Roy. Soc.*, 1952, *A*, **215**, 416). The resulting mean value for ΔH_1 is 11,910 ± 100 cal./g.-ion, whence ΔH_2 = 10,940 ± 140 cal./g.-ion. The values of ΔH_1 and ΔH_2 are compared with others in Table 3.

Of the last four sets of values, only those of Berthelot were determined directly. The others are derived from the temperature variation of the ionisation constants. The agreement of these values with ours is satisfactory.

TABLE 3. *Heat-content changes in reactions between hydrochloric acid and ethylenediamine.*

Source	ΔH_1	ΔH_2	Ref.
This work	11,910	10,940	
Everett and Pinsent	11,820	10,870	*Loc. cit.*
Williams	13,100	10,150	Thesis, Oxford, 1948
Dickens	11,450	10,900	Personal communication
Berthelot	12,400	10,800	*Ann. Chim. Phys.*, 1900, **20**, 163

Results for the metal ion–ethylenediamine systems are given in Table 4. In general, in any of these systems, there are three complex ions to consider, namely $M(en)^{++}$, $M(en)_2^{++}$, and $M(en)_3^{++}$. To evaluate the heat of formation of each of them, it being assumed that the three

TABLE 4. *Heat of reaction between metals and ethylenediamine.*

M = No. of g.-ions of metal $\times 10^3$; B = no. of moles of ethylenediamine $\times 10^2$; V = total vol. (c.c.) of solution after mixing; Q = heat evolved (in cal.); ΔH = heat content increase per g.-ion of metal on formation of complex from metal and ethylenediamine.

	M	B	V	Q	ΔH
Nickel.					
1 [a]	4·916	1·742	972	136·6	
2	4·900	0·960	972	86·8	$Ni(en)^{++} = -15{,}000$ [b]
3	4·902	0·962	972	85·6	$Ni(en)_2^{++} = -17{,}250$ [b]
4	4·904	1·125	974	100·3	$Ni(en)_3^{++} = -28{,}010$ [b]
5	4·902	1·295	976	116·9	
Zinc.					
6 [a]	4·963	1·016	975	51·4	$Zn(en)^{++} = +9{,}800$
7	4·956	1·464	985	59·2	$Zn(en)_2^{++} = -11{,}450$
8	4·952	2·868	981	66·4	$Zn(en)_3^{++} = -18{,}460$
Cadmium.					
9 [a]	4·898	1·012	977	60·7	$Cd(en)^{++} = -1{,}200$
10	4·911	1·452	966	69·8	$Cd(en)_2^{++} = -13{,}330$
11	4·870	2·881	978	78·8	$Cd(en)_3^{++} = -19{,}700$
Copper.					
—	—	—	—	—	$Cu(en)_2^{++} = -25{,}160$ [c]

[a] This is the mean of the data for three almost identical experiments. [b] Mean of values calc. for the following combinations of Q values: 1, 2, 4; 1, 3, 4; 1, 4, 5; 2, 4, 5; 3, 4, 5. [c] By using a slight excess of ethylenediamine, copper ion is completely converted into $Cu(en)_2^{++}$. The individual values for four experiments under these conditions were: −25,280; −25,120; −24,920; −25,310.

stability constants are known, at least three determinations of the heat evolved for different ratios of metal ion and ligand must be made. These heats of formation cannot be evaluated with equal precision from our experiments, and in fact the figures obtained for the ions $M(en)^{++}$ are almost worthless since only very small amounts of these ions were formed under the conditions employed, which were such that the pH of the final solution invariably exceeded 8. [To convert appreciable quantities of the metal into $M(en)^{++}$ without precipitation of the hydroxide would have meant buffering the reaction to a much lower pH.] As it was particularly desirable to obtain the best possible estimates of the heat of formation of the ion $M(en)_2^{++}$, since a comparison could then be made for nickel, copper, zinc, and cadmium, at least three measurements were made for the last three metals of the heat evolved at fixed concentrations chosen so that as much of the ion $M(en)_2^{++}$ was formed as possible. With zinc and cadmium, the mean of the results of the set of three experiments was combined with the results of at least two other experiments at different concentrations to obtain values for the heats of formation of all the complex ions. In experiments with nickel, which forms a more stable 3 : 1 complex, three determinations were made of the heat change when the ethylenediamine was in a slight excess of this ratio. In the choice of stability constants we have had the benefit of the advice of Dr. H. M. N. H. Irving and Mr. J. E. Dickens, to whom we are very grateful. From plots of stability constants obtained by different workers against ionic strengths, the following values of stability constants have been selected as the best available for the ionic strengths used by us:

Nickel	$\log_{10}k_1 = 7{\cdot}32$	$\log_{10}k_2 = 6{\cdot}06$	$\log_{10}k_3 = 4{\cdot}1$
Zinc	$\log_{10}k_1 = 5{\cdot}50$	$\log_{10}k_2 = 4{\cdot}55$	$\log_{10}k_3 = 1{\cdot}35$
Cadmium	$\log_{10}k_1 = 5{\cdot}2$	$\log_{10}k_2 = 4{\cdot}2$	$\log_{10}k_3 = 1{\cdot}7$
Copper	$\log_{10}k_1 = 10{\cdot}72$	$\log_{10}k_2 = 9{\cdot}31$	

As mentioned earlier, a linear temperature–time relation in the after-period of a calorimetric experiment was normally reached very quickly, within 10 sec. of opening the bottle. For one

system, however, this steady state was only reached after about 3 min. This was the system nickel–ethylenediamine under conditions such that a small but appreciable amount of the ion $Ni(en)_3^{++}$ was formed in the presence of a larger amount of the ion $Ni(en)_2^{++}$. This suggests that the formation of one of the complex ions has an appreciable activation energy. If the addition of the ethylenediamine molecules takes place in stages, it might be expected that that with the largest activation energy would be the final one in which the third molecule of ethylenediamine enters the complex if, as is probable, this involves the formation of an ion with three octahedrally disposed diamine molecules from one with two planar diamine molecules. All signs of the slow reaction disappeared in the presence of excess of ethylenediamine above that required for the stoicheiometric formation of the 3 : 1 complex, presumably because of a simple mass-action effect.

Discussion

In Table 5 are given our values of ΔH, the values of ΔG corresponding to the values of the formation constants already quoted, and the derived values of ΔS. These quantities refer to the formation of the complex ion at 25° in water containing neutral salt to give an ionic strength of 0·1. In the column headed $(\Delta S + S_{aq.})$, $S_{aq.}$ is the standard entropy of the cation. The following values for $S_{aq.}$ have been taken from Powell and Latimer (*J. Chem. Phys.*, 1951, **19**, 1139): Cu^{++} −23·6; Zn^{++} −25·45; Cd^{++} −14·6 cal./° c. They do not quote a figure for Ni^{++}. For this ion, Rossini (*op. cit.*) gives −38·1, which is described as a calculated value though the details are not given. This seems a surprisingly large (negative) value. A figure of −29·3 cal./° c was proposed by Barvinok (*J. Gen. Chem., U.S.S.R.*, 1950, **20**, 208), and as this seems more likely we have used it in evaluating $(\Delta S + S_{aq.})$ for nickel in Table 5: but even this figure of −29·3 is lower than that of any of the neighbouring transition metals.

Values of $(\Delta S + S_{aq.})$ are not, of course, the actual entropies of the complex ions on the conventional scale, but they are in the same relation as these entropies for ions of the same metal : amine ratio. Thus, the values of $(\Delta S + S_{aq.})$ for the ions $M(en)_2^{++}$ all differ by a constant amount from the standard entropies of these ions. The values for the ions $M(en)_3^{++}$ may similarly be compared with each other, but not with those for the ions $M(en)_2^{++}$.

Results for the 1 : 1 complex ions have been omitted from Table 5, since they are too inaccurate to justify their inclusion and discussion. We must once more stress that, owing to uncertainty in the values for some of the stability constants, there may be errors of several units in some of the ΔS values.

The entropy of an ion in solution depends on its interaction with the solvent molecules. If this is essentially electrostatic, then the greater the ionic size the less powerful is the field of force near the ion, and hence the interaction with neighbouring molecules is weaker. So the larger the ion, the larger its entropy: the quantitative relationship has been discussed by Powell and Latimer (*loc. cit.*). Thus the standard entropy of the cadmium ion exceeds that of the zinc ion by nearly 11 e.u. On the other hand, if we consider the ions $Zn(en)_3^{++}$ and $Cd(en)_3^{++}$, in which the metallic atom is surrounded by three octahedrally co-ordinated ethylenediamine molecules, these ions are much larger than the simple cations, and moreover, although the ion containing cadmium is presumably still the bigger of the two, the relative difference in size is now very much less. We must therefore expect that the standard entropies of these complex ions (after allowance for the contribution from the internal degrees of freedom of the chelated molecules) will not only be much larger than those of the simple ions, but will also be much more nearly equal. In fact, $(\Delta S + S_{aq.})$ is approximately the same for the ions $Zn(en)_2^{++}$ and $Cd(en)_2^{++}$, while for the 1 : 3 ions of these two elements the difference of 5 e.u. may well be due to errors in the formation-constant values. It is interesting that ΔH is numerically greater for the two complex cadmium ions than for the corresponding zinc ions, while the reverse is true of ΔG. It is probable that the interaction of transition-metal ions with water, and still more with amines, is not a simple electrostatic interaction, but that some degree of covalent bonding is involved. From the general chemical behaviour of zinc and cadmium, we should expect that covalent bonding would play a larger part with cadmium than with zinc, and hence that cadmium would form relatively stronger bonds with ethylenediamine than zinc. It is therefore not surprising

that the cadmium complexes are formed with a greater evolution of heat than are those containing zinc. That the latter are nevertheless the more stable is due to the entropy term ΔS. This is larger for zinc than for cadmium because the entropy gain when the water molecules surrounding the metallic ion are replaced by ethylenediamine molecules is greater for the smaller ion.

For the other 1 : 3 ion in Table 5, namely $Ni(en)_3^{++}$, $(\Delta S + S_{aq.})$ is markedly different from the values for the zinc and cadmium analogues. Unfortunately, as already stated, there is some ambiguity about the value of $S_{aq.}$ for nickel, and a redetermination of this quantity as well as a re-examination of the formation constants of the ethylenediamine complexes would be desirable.* It must, however, not be forgotten that we can only

TABLE 5. *Thermodynamic data for metal complexes of ethylenediamine.*

	ΔH	ΔG	ΔS	$(\Delta S + S_{aq.})$		ΔH	ΔG	ΔS	$(\Delta S + S_{aq.})$
$Ni(en)_2^{++}$	−17,250	−18,250	+ 3·4	−25·9	$Cd(en)_2^{++}$	−13,330	−12,820	− 1·7	−16·3
$Ni(en)_3^{++}$	−28,010	−23,840	−14·0	−43·3	$Cd(en)_3^{++}$	−19,700	−15,140	−15·3	−29·9
$Zn(en)_2^{++}$	−11,450	−13,710	+ 7·6	−17·9	$Cu(en)_2^{++}$	−25,160	−27,280	+ 7·1	−16·5
$Zn(en)_3^{++}$	−18,460	−15,550	− 9·8	−35·3					

expect the entropies of the ions $M(en)_3^{++}$ to be equal if they have identical shapes. If, in an ion of this type, two ethylenediamine molecules are strongly bound, but the third only weakly, it is possible that this last molecule would be attached at one end only. The entropy of such an ion need not then be the same as that of an ion in which all three ethylenediamine molecules are chelated. Of the three ions under discussion, the most stable is that formed by nickel, and though the cadmium and zinc complexes are weaker it is doubtful if the differences in ΔG for the 1 : 2 and 1 : 3 zinc and cadmium ions are small enough to make it likely that the third molecule is only attached to the metal at one nitrogen atom.

Turning to the ions of formula $M(en)_2^{++}$, these can now differ in shape and so need not necessarily have almost the same entropies. Thus, we should expect that the two ethylenediamine molecules in a $Cu(en)_2^{++}$ ion in solution are coplanar, whereas in a $Zn(en)_2^{++}$ ion in solution they are probably tetrahedrally disposed round the zinc. The interaction of the complex ion with water molecules may differ according to whether it is planar or tetrahedral. Thus, two water molecules might get fairly close to the metal ion in the planar complex by filling the two vacant octahedral sites, which is not possible with the tetrahedral ion. The extent to which the complex ion orders neighbouring water molecules (and also the extent to which it disorganises the water structure) will therefore depend on its shape; $(\Delta S + S_{aq.})$ is, in fact, about the same for the planar $Cu(en)_2^{++}$ as for the (probably) tetrahedral $Zn(en)_2^{++}$ and $Cd(en)_2^{++}$, while once again it appears to be the nickel ion which is out of line. It seems, therefore, that the entropies of the two types of 1 : 2 ion do not differ very much: but it would be very interesting to have really accurate relative entropy figures for a larger number of these ions, to see if in fact these entropies tend to fall into two groups, according to the shape of the complex.

In the Irving–Williams stability order (Irving and Williams, *Nature*, 1948, **162**, 746; *J.*, 1953, 3192), the stability of complexes of the first group of transition metals reaches a maximum with copper. For the ethylenediamine complexes, this is because ΔH is numerically largest for copper, which therefore forms stronger bonds with nitrogen than do nickel and zinc. The ΔH values of Table 5 can be regarded as being the relatively small differences between the interaction energies of the unhydrated (*i.e.*, gaseous) metal ion with water on the one hand, and ethylenediamine on the other. Relative values of the heats of hydration of a series of bivalent metal cations can be evaluated if we know for each metal its heat of vaporisation, its first and second ionisation potentials, and the heat of formation of one particular compound (the same compound for all the metals) in dilute aqueous solution. (The values so obtained differ slightly according to the compound chosen, but probably the

* Dr. Irving has pointed out to us that, on using Powell and Latimer's relation (*loc. cit.*) between ionic radius and entropy, the entropy of the nickel ion corresponding to the radius of 0·70 Å given by Pauling (" The Nature of the Chemical Bond," Cornell Univ. Press, 1945) is −24·9 e.u., and that if this value is used for $S_{aq.}$ instead of that of −29·3 e.u. which we have employed, the resulting figures for $(\Delta S + S_{aq.})$ for both nickel complexes are in much better agreement with those for the other metal complexes studied.

figures for the chlorides are the most reliable. The relation between the values about to be given is not qualitatively changed, however, by choosing other compounds for which the required information is available.) Using data from Rossini's book (*op. cit.*) for the chlorides of the transitional elements and taking −67 kcal. for the heat of hydration of the chloride ion (Kortum and Bockris, " Textbook of Electrochemistry," Elsevier Publishing Co., 1951, Vol. I, p. 124), we have the following heat of hydration figures (in kcal.): Mn^{++}, −483; Fe^{++}, −503; Co^{++}, −530; Ni^{++}, −545; Cu^{++}, −539; Zn^{++}, −529·5. In arriving at these values we have made use of recent determinations of the latent heats of evaporation of iron, cobalt, and copper carried out by Edwards, Johnston, and Ditmars (*J. Amer. Chem. Soc.*, **1951**, **73**, 4729; **1953**, **75**, 2467). The ion which hydrates with the greatest evolution of heat is nickel, not copper. This to some extent offsets the difference in the ΔH figures for nickel and copper in Table 5. But by combining these ΔH figures with those for the heats of hydration, we have that for the process

$$M^{++}(g.) + 2(en)(aq.) \rightleftharpoons M(en)_2{}^{++}(aq.)$$

ΔH is −562 for Ni; −564 for Cu; and −541 kcal. for Zn, so that copper must still be regarded as forming the strongest bonds with ethylenediamine.

Finally, for zinc and cadmium the ratio of the ΔH values for the 1 : 3 and 1 : 2 complexes is roughly 3 : 2, and the ratio for nickel is somewhat greater. But the corresponding ratio for the ΔG values is considerably less than 3 : 2. The reason for this is that, whereas the reaction of the hydrated metal ion to give the $M(en)_2{}^{++}$ is accompanied by an entropy increase (or with cadmium by only a *small* entropy decrease), the last stage in the formation of the $M(en)_3{}^{++}$ ion, *i.e.*, the reaction $M(en)_2{}^{++} + (en) \rightleftharpoons M(en)_3{}^{++}$, involves an entropy decrease, which with zinc and nickel amounts to 17·4 e.u. and with cadmium to 13·6 e.u. That the entropy change on formation of the $M(en)_2{}^{++}$ ion is positive (or if negative is small) is due, of course, to the release of water molecules from the hydrated ion. Since the entropy change is negative and quite large for the addition of a third ethylenediamine molecule, it would seem as if the further dehydration of the ion in this stage is a comparatively minor matter, and this is presumably why the values of $(\Delta S + S_{aq.})$ for the planar $Cu(en)_2{}^{++}$ and the presumably tetrahedral zinc and cadmium analogues are almost the same, notwithstanding what has been said on the possible dependence of entropy on ionic shape. Most of the entropy decrease of 15—17 e.u. in the third stage for nickel, zinc, and cadmium must therefore be derived from the reduction in the freedom of movement of the ethylenediamine molecule when it enters the complex.

We thank Mr. R. A. Care for assisting with some of the measurements, and Imperial Chemical Industries, Ltd., for financial help.

Inorganic Chemistry Laboratory,
South Parks Road, Oxford.

[*Received, February 3rd,* **1954**.]

Cyclisation of Benzamido-derivatives of 1 : 1′-*Dianthraquinonylamine to Derivatives of* 1 : 2-7 : 8-*Diphthaloylcarbazole.*

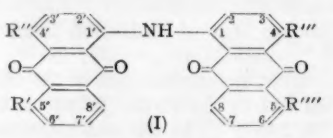
By William Bradley and Jeffrey V. Butcher.

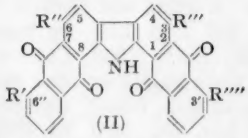
[Reprint Order No. 5185.]

On being heated with concentrated sulphuric acid the 4 : 4′-, 4 : 5′-, and 5 : 5′-dibenzamido-derivatives of 1 : 1′-dianthraquinonylamine are transformed into dibenzamido-derivatives of 1 : 2-7 : 8-diphthaloylcarbazole.

In 1910 Mieg (G.P. 239,544) showed that on being heated with concentrated sulphuric acid at 30—40° 4 : 5′-dibenzamido-1 : 1′-dianthraquinonylamine (I; $R' = R''' = NHBz$, $R'' = R'''' = H$) gave a brown colouring matter, and that similar treatment of the 4 : 4′-isomer (I; $R'' = R''' = NHBz$, $R' = R'''' = H$) gave an olive dye. Mieg regarded his products as acridines formed by dehydration, but it was found later (G.P. 464,292) that the olive dye resulted also from 1 : 2-7 : 8-diphthaloylcarbazole (II) by nitration, reduction,

and benzoylation. Thereafter both the olive and the brown dye and an analogous orange-yellow product from 5 : 5′-dibenzamido-1 : 1′-dianthraquinonylamine (I; R′ = R′′′′ = NHBz, R″ = R‴ = H) (G.P. 239,544; Swiss P. 115,114) came to be regarded as derivatives of carbazole.


(I)


(II)

In the present experiments the three dibenzamido-derivatives of 1 : 1′-dianthraquinonylamine have been prepared in pure condition, further characterised, and converted into the products described in the patents mentioned. The final products have been described in greater detail, analysed, and then converted by removal of benzoyl groups and resulting amino-groups into 1 : 2-7 : 8-diphthaloylcarbazole (II; R′ = R″ = R‴ = R′′′′ = H), identical with the compound prepared by Bradley and Thitchener (*J.*, 1953, 1085). The carbazole structure of the three colouring matters is thus confirmed, and with this the remarkable dehydrogenation and cyclisation of substituted 1 : 1′-dianthraquinonylamines by means of warm concentrated sulphuric acid.

The three dibenzamido-derivatives of 1 : 1′-dianthraquinonylamine were prepared essentially by the methods of G.P. 162,824 and 220,581. They were debenzoylated by hot phosphoric acid; there was no evidence of cyclisation in this reaction. Deamination was by diazotization and treatment with hypophosphorous acid.

Heating with phosphoric acid provides a convenient means of hydrolysing many *N*-acylaminoanthraquinones; several examples are given in the Experimental portion.

Experimental

5 : 5′-*Dibenzamido*-1 : 1′-*dianthraquinonylamine*.—A sample of 1-amino-5-benzamidoanthraquinone had m. p. 249° after crystallisation from chlorobenzene (Found: N, 8·05. Calc. for $C_{21}H_{14}O_3N_2$: N, 8·19%). Hefti (*Helv. Chim. Acta*, 1931, **14**, 1404) records m. p. 244—245°. 1-*Benzamido*-5-*chloroanthraquinone* crystallised from chlorobenzene as golden-yellow needles, m. p. 218° (Found: N, 3·9; Cl, 9·7. $C_{21}H_{12}O_3NCl$ requires N, 3·9; Cl, 9·8%). 5 : 5′-*Dibenzamido*-1 : 1′-*dianthraquinonylamine*, prepared by heating 1-amino-5-benzamidoanthraquinone with 1-benzamido-5-chloroanthraquinone in nitrobenzene with copper chloride, sodium acetate, and sodium carbonate, crystallised (Soxhlet) from chlorobenzene in fine, dark red needles, m. p. > 360° (Found: C, 75·6; H, 3·7; N, 6·3. $C_{42}H_{25}O_6N_3$ requires C, 75·6; H, 3·8; N, 6·3%). The solution in concentrated sulphuric acid was green; addition of 40% formaldehyde solution changed the colour to blue. The red solution in pyridine became yellow-brown on the addition of methanolic potassium hydroxide.

3′ : 6′′-*Dibenzamido*-1 : 2-7 : 8-*diphthaloylcarbazole* (II; R′ = R′′′′ = NHBz, R″ = R‴ = H).—The orange product obtained by heating 5 : 5′-dibenzamido-1 : 1′-anthraquinonylamine with concentrated sulphuric acid at 30—35° was heated with aqueous sodium dichromate solution, then with sodium hydrogen sulphite, as described in B.I.O.S. Final Report, No. 1493, p. 17 (London, H.M.S.O.). Finally, it was washed, dried, and crystallised from 1 : 2 : 4-trichlorobenzene (Found: C, 76·1, 75·6; H, 4·3, 2·9; N, 6·1. Calc. for $C_{42}H_{23}O_6N_3$: C, 75·8; H, 3·5; N, 6·3%). The purified derivative was very sparingly soluble in dimethyl phthalate and in 1 : 2 : 4-trichlorobenzene. Absorption max. in "AnalaR" sulphuric acid: 323 (ε 5·08 × 10^4), 640 mμ (ε 5·97 × 10^4). The blue solution in this medium was initially unchanged by the addition of 40% aqueous formaldehyde but a grey violet colour developed after a few minutes. A solution in trichlorobenzene gave a single, strongly absorbed, orange band when chromatographed on alumina.

Another preparation of the colouring matter in which the treatment with dichromate and bisulphite was omitted and the product was crystallised from dimethyl phthalate gave the same result.

Hydrolysis.—The foregoing compound (0·54 g.) was heated at 180—190° for 7 hr. with syrupy phosphoric acid (30 c.c.; *d* 1·75), which had been heated previously to 240° until foaming ceased. The resulting solution was cooled and added to water, and the insoluble portion was

collected and washed in turn with water, aqueous sodium carbonate, and water, and then dried (0·38 g.). The 3′ : 6″-diamino-1 : 2-7 : 8-diphthaloylcarbazole separated from 1 : 2 : 4-trichlorobenzene as a dull, reddish-orange solid, which sublimed *in vacuo* to give a single band of the same colour.

Deamination.—A solution of the diamine (1·2 g.) in 96% sulphuric acid (20 c.c.) was added at 0—5° to one of nitrosylsulphuric acid prepared from sodium nitrite (0·4 g.) and 96% sulphuric acid (20 c.c.). After being stirred for 1·5 hr. the resulting solution was added to 200 g. of crushed ice. The bisdiazonium salt separated in part, leaving an orange solution. After 0·5 hr. hypophosphorous acid (20 c.c. of 30%) was slowly added (0·5 hr.) at —5° and then stirring was continued for 2·5 hr. After 12 hr. at 0° the insoluble product was collected, washed neutral, dried (1·1 g.), and sublimed *in vacuo*. The orange-yellow needles formed (Found : C, 78·7; H, 3·2; N, 3·3. Calc. for $C_{28}H_{13}O_4N$: C, 78·7; H, 3·0; N, 3·3%) showed the following absorption maxima in concentrated sulphuric acid : 270 (ε 3·34 × 10^4) and 510 mμ (ε = 1·97 × 10^4), and were shown by direct comparison to be identical with 1 : 2-7 : 8-diphthaloylcarbazole (Found, in authentic sample : C, 78·8; H, 3·1; N, 3·5%. Absorption in concentrated sulphuric acid : max. 270 (ε 3·41 × 10^4), 510 mμ (ε 2·15 × 10^4).

4 : 5′-*Dibenzamido*-1 : 1′-*dianthraquinonylamine.*—1-Benzamido-4-chloroanthraquinone crystallised from chlorobenzene as golden-yellow needles, m. p. 238° (Found : N, 3·9; Cl, 9·4. Calc. for $C_{21}H_{12}O_3NCl$: N, 3·9; Cl, 9·8%); Bedekar, Tilak, and Venkataraman (*Proc. Indian Acad. Sci.*, 1948, **28**, 249) state m. p. 240°. When it was condensed with 1-amino-5-benzamidoanthraquinone by the method adopted for the preparation of the 5 : 5′-isomer the result was a dark solid. The 4 : 5′-*dibenzamido-amine* separated from nitrobenzene or *o*-dichlorobenzene as granules having a slightly bronzy lustre, but well-defined crystals were not obtained. The olive-green solution in concentrated sulphuric acid became darker and blue-green in colour on the addition of formaldehyde. The wine-red solution in pyridine became grey with a drop of methyl-alcoholic potassium hydroxide (Round : C, 73·6; H, 3·8; N, 6·5. $C_{42}H_{25}O_6N_3$ requires C, 75·6; H, 3·8; N, 6·3%).

3 : 6″-*Dibenzamido*-1 : 2-7 : 8-*diphthaloylcarbazole* (II; R′ = R‴ = NHBz, R″ = R⁗ = H).—The foregoing product was stirred for 7 hr. at 20—25° with 96% sulphuric acid and 20% oleum. The resulting solution was added to water containing sodium chlorate and heated as described in B.I.O.S. Final Report, No. 1493, p. 13. The insoluble 3 : 6″-*dibenzamido-carbazole* furnished a red-brown powder which was extremely sparingly soluble in 1 : 2 : 4-trichlorobenzene or dimethyl phthalate (Found : C, 75·2; H, 3·7; N, 6·0. $C_{42}H_{23}O_6N_3$ requires C, 75·8; H, 3·5; N, 6·3%). A solution in concentrated sulphuric acid showed absorption max. at 343 (ε 4·47 × 10^4), 560 (ε 3·54 × 10^4), and 605 mμ (ε 3·82 × 10^4). The bluish-red solution remained unaltered at first on the addition of formaldehyde but after a few minutes it became grey. The same product was obtained when 4 : 5′-dibenzamido-1 : 1′-dianthraquinonylamine was treated with 98% sulphuric acid only, the subsequent treatment with sodium chlorate being omitted. Absorption in concentrated sulphuric acid : max. 343 (ε 4·27 × 10^4), 560 (ε 3·48 × 10^4), and 605 mμ (ε 3·95 × 10^4).

Hydrolysis.—Following the procedure used for the orange isomer, the above red-brown colouring matter (0·88 g.) was heated for 7 hr. at 180—190° with syrupy phosphoric acid (30 c.c.; *d* 1·75). Benzoic acid sublimed. The resulting diamine was a dark brown solid (0·61 g.) which was very sparingly soluble in 1 : 2 : 4-trichlorobenzene. It sublimed with difficulty *in vacuo* with formation of purplish-black needles.

Deamination.—A solution of the diamine (0·6 g.) in concentrated sulphuric acid (20 c.c.) was diazotized as described above by means of nitrosylsulphuric acid prepared from sodium nitrite (0·2 g.) and concentrated sulphuric acid (20 c.c.). The precipitated bisdiazonium salt was reduced as above. The product (0·55 g.) was a light brown powder which dissolved in hot 1 : 2 : 4-trichlorobenzene with a yellow colour and on sublimation gave orange-yellow needles of 1 : 2-7 : 8-diphthaloylcarbazole (Found : N, 3·5. Calc. for $C_{28}H_{13}O_4N$: N, 3·3%). A solution in concentrated sulphuric acid exhibited max. at 270 (ε 3·41 × 10^4) and 510 mμ (ε 2·02 × 10^4).

4 : 4′-*Dibenzamido*-1 : 1′-*dianthraquinonylamine.*—The crude product obtained by condensing 1-benzamido-4-chloroanthraquinone with 1-amino-4-benzamidoanthraquinone (Il'inski and Saikin, *Zentr.*, 1934, I, 1041) was washed with alcohol, and extracted in turn with hot dilute ammonia and then water. Crystallisation from nitrobenzene gave the 4 : 4′-*dibenzamido-amine* as dark, lustrous needles which were green by transmitted and purple by reflected light (Found : C, 75·4; H, 3·8; N, 6·3. $C_{42}H_{25}O_6N_3$ requires C, 75·6; H, 3·8; N, 6·3%). This product was identical with the compound prepared by the following means. 1-Aminoanthraquinone was condensed with 1-chloroanthraquinone to give 1 : 1′-dianthraquinonylamine

(Found : C, 78·7; H, 3·6; N, 3·4. Calc. for $C_{28}H_{15}O_4N$: C, 78·3; H, 3·5; N, 3·3%). Nitration according to Eckert and Stei ner(*Monatsh.*, **1913**, **123**, IIb, 625) gave a red-brown dinitro-compound which crystallised from nitrobenzene in orange needles (Found : C, 64·6; H, 3·4; N, 7·8. Calc. for $C_{28}H_{13}O_8N_3$: C, 64·7; H, 2·5; N, 8·1%). Reduction with sodium sulphide gave the diamino-compound, and this crystallised from *o*-dichlorobenzene in very dark purple, almost black, plates (Found : C, 72·4; H, 3·5; N, 8·7. Calc. for $C_{28}H_{17}O_4N_3$: C, 73·2; H, 3·7; N, 9·2%). On being heated with benzoyl chloride (1 c.c.) in *o*-dichlorobenzene (15 c.c.) at 150° for 3 hr. the diamine (1 g.) gave 1·45 g. of 4 : 4′-dibenzamido-1 : 1′-dianthraquinonylamine, which after crystallisation from *o*-dichlorobenzene was identical (Found : N, 6·5%) with the compound obtained by condensing 1-benzamido-4-chloroanthraquinone with 1-amido-4-benzamidoanthraquinone.

3 : 6-*Dibenzamido*-1 : 2-7 : 8-*diphthaloylcarbazole* (II; R″ = R‴ = NHBz, R′ = R⁗ = H).—The *product* obtained by stirring 4 : 4′-dibenzamido-1 : 1′-dianthraquinonylamine with concentrated sulphuric acid at 25—30°, and addition to aqueous sodium chlorate (B.I.O.S. Final Report No. 1493, p. 31) was a dark blue-green powder. Crystallisation from dimethyl phthalate gave minute, dark blue-green needles (Found : C, 75·3; H, 3·5; N, 6·4. $C_{42}H_{23}O_6N_3$ requires C, 75·8; H, 3·5; N, 6·3%). A solution in concentrated sulphuric acid showed max. at 268 (ε 4·42 × 10^4), 365 (ε 5·25 × 10^4), 380 (ε 5·2 × 10^4), 550—554 (ε 3·49 × 10^4), and 590 mμ (ε 3·71 × 10^4). This derivative is less soluble in boiling diethyl phthalate (0·07%) than in dimethyl phthalate (0·12%), and more separates from the dimethyl ester on cooling. Its identity with the compound prepared from 1 : 2-7 : 8-diphthaloylcarbazole by dinitration, reduction, and benzoylation (G.P. 464,292) was confirmed. It was also identical with the product obtained by stirring 4 : 4′-dibenzamido-1 : 1′-dianthraquinonylamine (0·5 g.) with concentrated sulphuric acid at the room temperature for 7 hr. (0·45 g.) and crystallising from diethyl phthalate. The absorption of a solution in concentrated sulphuric acid exhibited max. at 268 (ε 3·91 × 10^4), 365 (ε 5·28 × 10^4), 380 (ε 5·28 × 10^4), 550—554 (ε 3·13 × 10^4), and 590 mμ (ε 4·02 × 10^4).

Hydrolysis.—The above derivative (0·97 g.) was heated with syrupy phosphoric acid (30 c.c.; *d* 1·75) at 180—190° for 7 hr. as described on p. 2313 (yield, 0·67 g.).

Deamination.—A solution of the diamine (0·65 g.) in concentrated sulphuric acid (20 c.c.) was diazotized by means of nitrosylsulphuric acid from sodium nitrite (0·2 g.) and concentrated sulphuric acid (10 c.c.). After addition to crushed ice the bisdiazonium salt separated as an almost insoluble precipitate. The suspension was reduced with hypophosphorous acid to a sandy solid which was washed until neutral and dried (0·6 g.). Sublimation *in vacuo* gave clusters of orange yellow needles of 1 : 2-7 : 8-diphthaloylcarbazole (Found : N, 3·5. Calc. for $C_{28}H_{13}O_4N$: N, 3·3%). A solution in concentrated sulphuric acid showed absorption max at 270 (ε 3·42 × 10^4) and 510 mμ (ε 1·97 × 10^4).

Hydrolysis of Acylaminoanthraquinones.—By the procedure described on p. 2312 the following results were obtained :

Compound	Weight (g.)	Temp.	Time (hr.)	Benzoic acid (g.) Found *	Calc.
1-Amino-5-benzamidoanthraquinone †	0·913	170°	0·5	0·324	0·326
1-Benzamido-5-chloroanthraquinone	1·241	180	0·5	0·404	0·414
1-Amino-4-benzamidoanthraquinone	1·231	180	0·5	0·437	0·439
5 : 5′-Dibenzamido-1 : 1′-dianthraquinonylamine	0·562	180—200	1·5	0·121	0·205
	0·446	180—190	7·0	0·148	0·162

* Ether-extraction and sublimation.

† In this expt. the yield of 1 : 5-diaminoanthraquinone was 0·634 g. (calc. 0·635 g.).

We thank the University of Leeds for the award of a Hickson and Welch Research Scholarship to one of us (J. V. B.), and Imperial Chemical Industries Limited, Dyestuffs Division, Blackley, for gifts of intermediates.

CLOTHWORKERS' RESEARCH LABORATORY, UNIVERSITY OF LEEDS. [*Received, March 6th*, 1954.]

Acyclic Derivatives of Amino-sugars.

By M. W. Whitehouse, P. W. Kent, and C. A. Pasternak.

[Reprint Order No. 4208.]

Preparation of D-glucosamine diethyl mercaptal hydrochloride and *N*-acyl derivatives of the amine is described. Penta-acetyl-D-glucosamine diethyl mercaptal and mercuric chloride in aqueous acetone gave the *aldehydo*-sugar. The validity of certain diagnostic colour reactions is discussed. Analogous acyclic derivatives have been obtained from D-galactosamine.

Series of acyclic compounds of D-glucosamine and D-galactosamine have been prepared from the appropriate diethyl mercaptals in order to determine to what extent acyclic 2-amino-2-deoxy-hexoses are detectable in natural products by the usual amino-sugar tests. Since some of the results reported in our preliminary communication (Kent, *Research*, 1950, **3**, 427) have been disputed by Wolfrom and Anno (*J. Amer. Chem. Soc.*, 1952, **74**, 6150), we now give a fuller account and extend our description to derivatives of galactosamine.

Desulphurisation of penta-acetyl-D-glucosamine diethyl mercaptal (Wolfrom, *J. Amer. Chem. Soc.*, 1929, **51**, 2188) gave *aldehydo*-penta-acetyl-D-glucosamine, which was separated chromatographically on a powdered cellulose column (Hough, Hirst, and Jones, *J.*, 1949, 250). A solution of the *aldehydo*-sugar in an acetate buffer (pH 3·34; 0·02 mg. of sugar per ml.) had an absorption band at 265 mμ similar to that of *aldehydo*-penta-*O*-acetyl-glucose and -galactose under the same conditions (Pascu and Hillier, *J. Amer. Chem. Soc.*, 1948, **70**, 523). The *aldehydo*-sugar strongly reduced Fehling's solution, restored the colour to Schiff's reagent, gave an Elson–Morgan colour reaction, and formed a crystalline phenylhydrazone.

These mercaptals could be detected on paper chromatograms by the use of iodine vapour (Brante, *Nature*, 1949, **163**, 651: Greenway, Kent, and Whitehouse, *Research*, 1953, **6**, 6S). D-Glucosamine diethyl mercaptal hydrochloride gave the ninhydrin reaction and *aldehydo*-penta-*O*-acetyl-D-glucosamine was detected with aniline hydrogen phthalate (Partridge, *Nature*, 1949, **164**, 443). Acyclic derivatives of these types are not normally detected by the Molisch, Elson–Morgan, or Dische–Borenfreund colour tests.

Experimental

Chromatography was performed on Whatman No. 1 paper in *n*-butanol–ethanol–water (4 : 1 : 5).

2-Amino-2-deoxy-D-glucose Diethyl Mercaptal Hydrochloride (*D-Glucosamine Diethyl Mercaptal Hydrochloride*).—D-Glucosamine hydrochloride (10 g.) was shaken with fuming hydrochloric acid (80 ml., saturated at 0°) and ethanethiol (30 ml.) overnight or until completely dissolved. Ethanol (70 ml.) and lead carbonate were added and the neutral filtrate was concentrated to small bulk. The product (70%), when recrystallised from aqueous alcohol, had m. p. 75—76°, $[\alpha]_D^{20}$ −18·5° (*c*, 0·2 in H_2O), R_F 0·72 (Found: C, 37·05; H, 7·4; N, 4·1; S, 19·6. Calc. for $C_{10}H_{24}O_4NS_2Cl$: C, 37·2; H, 7·45; N, 4·35; S, 19·9%).

2-Acetamido-2-deoxy-D-glucose Diethyl Mercaptal.—(i) The mercaptal hydrochloride (8 g.) in dry methanol (50 ml.) and acetic anhydride (6 g.) was shaken with powdered silver acetate (6·5 g.) at room temperature for 3 hr. and finally boiled for 5 min. The filtrate was concentrated under reduced pressure to a syrup which crystallised readily. The product, recrystallised from ethanol–benzene, had m. p. 129°.

(ii) The hydrochloride (5 g.) in absolute ethanol (70 ml.) was treated with sodium (0·35 g.). Excess of keten (2 g.) (Herriot, *J. Gen. Physiol.*, 1934, **18**, 69) was passed into the filtered solution. The product recrystallised from ethanol–light petroleum as white plates, m. p. 122—123°, $[\alpha]_D^{19}$ −37° (*c*, 0·96 in H_2O), R_F 0·81 (Found: C, 44·0; H, 7·6; N, 4·2; S, 19·2. Calc. for $C_{12}H_{25}O_5NS_2$: C, 44·0; H, 7·6; N, 4·3; S, 19·6%).

N-Benzyloxycarbonyl-D-glucosamine Diethyl Mercaptal.—D-Glucosamine diethyl mercaptal hydrochloride (5 g.) in water (50 ml.) containing sodium hydrogen carbonate (3·5 g.) was treated with benzyl chloroformate (3·5 ml.). *N-Benzyloxycarbonyl-D-glucosamine diethyl mercaptal*

(6·8 g.), which separated at 0°, recrystallised from aqueous alcohol or benzene as white plates, m. p. 94°, $[\alpha]_D^{21}$ −28° (*c*, 0·29 in EtOH), R_F 0·90 (Found: C, 51·2; H, 7·0; N, 3·4; S, 15·5. $C_{18}H_{29}O_6NS_2$ requires C, 51·4; H, 6·9; N, 3·3; S, 15·3%).

*Pentamethyl-*D*-glucosamine Diethyl Mercaptal.*—The mercaptal hydrochloride (3·2 g.) in dioxan (50 ml.) was treated with sodium chloride (6 g. in 15 ml. of water) and methyl sulphate (3·8 ml.). After addition of solid carbon dioxide, the mixture was heated to the b. p., neutralised with sulphuric acid, and extracted repeatedly with chloroform. The extract of *methyl* derivative was dried ($MgSO_4$) and concentrated to a syrup, $[\alpha]_D^{21}$ −15·8° (*c*, 0·4 in $CHCl_3$) (Found: OMe, 34·6. $C_{15}H_{33}O_4NS_2$ requires OMe, 34·9%).

N-*Benzoyl-*D*-glucosamine Diethyl Mercaptal.*—Glucosamine diethyl mercaptal hydrochloride (0·5 g.) was treated with redistilled pyridine (5 ml.) and benzoyl chloride (0·5 ml.) and after 12 hr. poured into ice-water. The precipitate of N-*benzoyl-*D*-glucosamine diethyl mercaptal*, washed with water and recrystallised from aqueous ethanol, had m. p. 130—131°, $[\alpha]_D^{21}$ −18° (*c*, 0·23 in EtOH), R_F 0·98 (Found: C, 51·9; H, 6·9; N, 3·5; S, 15·9. $C_{17}H_{27}O_5NS_2$ requires C, 52·4; H, 6·9; N, 3·6; S, 16·4%).

Attempted O-*Benzoylation of Glucosamine Diethyl Mercaptal.*—Treatment of the diethyl mercaptal hydrochloride with excess of benzoyl chloride yielded a product, m. p. 79—80° [C, 62·2; H, 5·25; N, 1·8; S, 9·2. Calc. for $C_{45}H_{43}O_9NS_2$ (the pentabenzoyl mercaptal): C, 67·2; H, 5·3; N, 1·7; S, 7·95%]. Repeated crystallisation yielded a product, m. p. 129—130° alone or mixed with *N*-benzoylglucosamine diethyl mercaptal.

N-*Acetyl-tetra-*O*-benzoylglucosamine Diethyl Mercaptal.*—*N*-Acetylglucosamine diethyl mercaptal (0·5 g.) was dissolved in redistilled pyridine containing benzoyl chloride (1·2 ml.) and after 24 hr. poured into ice-water. The *penta-acyl* derivative, recrystallised from aqueous alcohol, had m. p. 141—143°, $[\alpha]_D^{22}$ +5 (*c*, 0·5 in $COMe_2$) (Found: C, 64·1; H, 5·6; N, 1·7; S, 9·2. $C_{40}H_{41}O_9NS_2$ requires C, 64·6; H, 5·5; N, 1·9; S, 8·6%).

*Penta-acetyl-*D*-glucosamine Diethyl Mercaptal.*—*N*-Acetylglucosamine diethyl mercaptal (2 g.) was treated with acetic anhydride (5 ml.) in pyridine (20 ml.) and after 24 hr. poured into ice-water. The mixture was extracted with chloroform, and the extracts were washed repeatedly with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water before being dried (Na_2CO_3). Evaporation gave a syrup which crystallised from ethanol–light petroleum (b. p. 60—80°). The *mercaptal*, crystallised from chloroform–light petroleum, had m. p. 177°, $[\alpha]_D^{20}$ −36·5° (*c*, 0·5 in $CHCl_3$), R_F 0·95 (Found: C, 48·5; H, 6·7; N, 2·8. $C_{20}H_{33}O_9NS_2$ requires C, 48·5; H, 6·7; N, 2·8%). Wolfrom, Lemieux, and Olin (*J. Amer. Chem. Soc.*, 1949, **71**, 2870) reported m. p. 126—127°, $[\alpha]_D^{22}$ −32° (in $CHCl_3$), which Wolfrom and Anno (*ibid.*, 1952, **74**, 6150) corrected to m. p. 75—77°, $[\alpha]_D$ +1°.

2-*Acetamido-*3 : 4 : 5 : 6-*tetra-*O*-acetyl-*2*-deoxy-*D*-glucose* (*Penta-acetyl-*aldehydo-D*-glucosamine*).—To penta-acetyl-D-glucosamine diethyl mercaptal (2·9 g.) in 30% aqueous acetone (60 ml.), cadmium carbonate (20 g.) and mercuric chloride (5 g.) in acetone (30 ml.) were added. After 24 hr. the mixture was heated at 50° for 15 min. and finally at the b. p. for 15 min. The filtrate was freed from traces of a mercury complex by chromatography on powdered cellulose with *n*-butanol–ethanol–water (4 : 1 : 5) as eluant (Hough, Jones, and Wadman, *J.*, 1949, 2511). The product was detected in the effluent by its colour with aniline hydrogen phthalate. The fractions containing aldehydo-*penta-acetylglucosamine* were concentrated to a syrup; crystallised from *iso*propyl ether this (0·2 g.) had m. p. 156—157° (decomp.), $[\alpha]_D^{21}$ +36·7° (*c*, 0·1 in $CHCl_3$), R_F 0·92 (Found: C, 49·1; H, 5·75; N, 3·3. $C_{16}H_{23}O_{10}N$ requires C, 49·3; H, 5·9; N, 3·6%).

2-*Amino-*2*-deoxy-*D*-galactose Diethyl Mercaptal Hydrochloride* (D*-Galactosamine Diethyl Mercaptal Hydrochloride*).—D-Galactosamine (0·5 g.) was treated with ethanethiol (2·5 ml.) and fuming hydrochloric acid (5 ml.) under the conditions described for glucosamine diethyl-mercaptal. The product (n_D^{22} 1·5302) failed to crystallise.

2-*Acetamido-*3 : 4 : 5 : 6-*tetra-*O*-acetyl-*2*-deoxy-*D*-galactose Diethyl Mercaptal.*—The preceding hydrochloride (0·5 g.) with acetic anhydride (2 ml.) in dry pyridine (4 ml.) gave the *amide*, m. p. 184° (from ethyl acetate), $[\alpha]_D^{20}$ −22 (*c*, 0·36 in $CHCl_3$), R_F 0·95 (Found: C, 49·0; H, 6·6. $C_{20}H_{33}O_9NS_2$ requires C, 49·5; H, 6·7%).

2-*Benzyloxycarbonylamino-*2*-deoxy-*D*-galactose Diethyl Mercaptal.*—The mercaptal hydrochloride was treated with benzyl chloroformate as in the preceding case. The *product* had m. p. 59—61°, $[\alpha]_D^{27}$ +33 (*c*, 0·3 in $CHCl_3$), R_F 0·88 (Found: C, 51·15; H, 6·8. $C_{18}H_{29}O_6NS_2$ requires C, 51·4; H, 6·9%).

Colour Reactions.—(i) *Molisch test.* The modification described by Devor (*J. Amer. Chem. Soc.*, 1950, **72**, 2008) was employed. No positive reaction (increased absorption at 570 mμ)

was given by pyranose forms of D-glucosamine (free sugar, glucosaminides) or by any of the acyclic derivatives in the concentration range 0·1—1·0 mg./ml. By contrast 3-amino-3-deoxyaltrose hydrochloride and 2-chloro-2-deoxyaltrose (kindly presented by Dr. L. F. Wiggins) gave strong colours under similar conditions.

(ii) *Elson–Morgan reaction* (*Biochem. J.*, 1933, **27**, 1824; 1934, **28**, 988). The diethyl mercaptals failed to give the characteristic colour reaction given by D-glucosamine hydrochloride and *N*-acetyl- and *N*-benzyloxycarbonyl-glucosamine. *aldehydo*-Penta-acetyl-D-glucosamine and the isomeric 1 : 3 : 4 : 6-tetra-*O*-acetyl-*N*-acetylglucosamine gave strong colours. 3-Amino-3-deoxyaltrose and 6-amino-6-deoxyglucose were without reaction. These findings appear to be in accordance with the findings of Morgan (*Chem. and Ind.*, 1938, **57**, 1191) and Morgan and King (*Biochem. J.*, 1943, **37**, 640).

(iii) *Dische–Borenfreund reaction* (*J. Biol. Chem.*, 1950, **184**, 517). D-Glucosamine diethyl mercaptal gave a pink colour in contrast to the orange colour from glucosamine and glucosaminide hydrochlorides, in concentrations of 0·1—1·0 mg./ml.

The authors thank Professor Sir Rudolph Peters, F.R.S., for his interest.

DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF OXFORD. [*Received, March 30th*, 1953.]

Kinetics and Mechanism of Aromatic Halogenation by Hypohalous Acids. Part I. Bromination of Aromatic Ethers by Hypobromous Acid.

By S. J. BRANCH and BRYNMOR JONES.

[Reprint Order No. 4920.]

The reactivity of hypobromous acid with aromatic ethers in 75% acetic acid at 19·8° is extremely high, and the rates become measurable only when the ethers contain one or more powerful deactivating substituents. The kinetics of the bromination of *p*-nitroanisole and *p*-nitrophenetole show that the reaction is bimolecular, and of first order with respect to each of the reactants.

The rate of substitution is much higher than with either bromine or bromine chloride in the same medium, although Derbyshire and Waters (*J.*, 1950, 564) found that at pH 7 the velocities of bromination of sodium *p*-anisate by bromine and by hypobromous acid are in the ratio 2000 to 1.

The formation of the hydrated bromine cation by the equilibrium $H^+ + HOBr \rightleftharpoons BrOH_2^+$ has been postulated to explain the acid-catalysed bromination of sodium toluene-ω-sulphonate, and a similar explanation is now advanced for the enhanced reactivity of hypobromous acid in 75% acetic acid solution. Experiment shows that the reaction with *p*-nitroanisole is catalysed by mineral acid, the value of $k_{bi}/[H^+]$ remaining virtually constant for $[H^+]$ in the range 0·005—0·090M.

A decrease in the rate of bromination on the addition of acetate ion to the solution, and an increase in rate in the presence of neutral salts, confirm that bromination by the brominium ion Br^+ or by the solvated cation $BrOH_2^+$ is of predominant importance in the medium used.

ALTHOUGH much attention has been given to the study of substitution by bromine, little was known until recently of the nature of the various brominating agents, or of the influence of solvents, particularly of acid media, in modifying their reactivity. As a result, the relative brominating powers of such agents have, through a conflict of evidence, remained obscure. This is especially true of molecular bromine, bromine water, and hypobromous acid (Bradfield and Brynmor Jones, *Trans. Faraday Soc.*, 1941, **37**, 734, and references cited therein).

It is generally accepted that the brominating power of a reagent Br–X is not only related to the electron affinity of X, but is also determined by its polarisability to the activated state, $\overset{\delta+}{Br}\text{–}\overset{\delta-}{X}$ (Ingold, Smith, and Vass, *J.*, 1927, 1245; Ingold, *Chem. Reviews*, 1934, **15**, 271). The brominium ion Br^+ should therefore be the most powerful, and

hypobromous acid one of the weakest of brominating agents. In acid media, however, hypobromous acid has been found to be a most effective reagent. This was first observed by Shilov and Kanjaev (*Doklady Akad. Nauk S.S.S.R.*, 1939, **24**, 890), who showed that in weakly alkaline solution the bromination of sodium anisole-*m*-sulphonate (ArH) by bromine-free hypobromous acid proceeds in accordance with the equation $d[HOBr]/dt = k_2[ArH][HOBr]$. On the addition of sulphuric or nitric acid k_2 increased in value, but $k_2/[H^+]$ remained approximately constant. The rate of reaction could be represented by $d[HOBr]/dt = k_1[ArH][HOBr][H^+]$, where $k_1 = k_2/[H^+]$, and $[HOBr][H^+]$ is a measure of the formation of the bromine cation, in accordance with the equilibrium, $H^+ + HOBr \rightleftharpoons H_2O + Br^+$. This view has been confirmed recently by Derbyshire and Waters (*loc. cit.*) for the bromination of sodium toluene-ω-sulphonate and of benzoic acid. In aqueous solution at pH 5·18, sodium toluene-ω-sulphonate is not attacked by bromine-free hypobromous acid at 21·5°, but on the addition of perchloric acid, and at pH 2, bromination becomes rapid, and is a reaction of the first order with respect to each reactant, and second order as a whole for 90% of the reaction. In the light of these results it becomes clear, as Derbyshire and Waters have pointed out, that the conflicting evidence relating to the relative effectiveness of bromine and hypobromous acid arises from the different acidities of the media used.

Direct confirmation of the presence of bromine cations in acidified solutions of hypobromous acid has been obtained from electrodialytic experiments by Gonda-Hunwald, Graf, and Körösy (*Nature*, 1950, **166**, 68), but thermodynamic calculations by Bell and Gelles (*J.*, 1951, 2734) have shown that the bare halogen cation cannot exist in appreciable concentration in aqueous solution, although the solvated cation is much more stable. If this, then, is the reagent in acid media, the bromination of aromatic compounds by hypobromous acid in the presence of added acid may be represented as follows:

$$\left.\begin{aligned} H^+ + HOBr &\overset{\text{Rapid}}{\rightleftharpoons} BrOH_2^+ \\ BrOH_2^+ + ArH &\xrightarrow{\text{Slow}} (ArH{\cdot}Br)^+ + H_2O \\ (ArH{\cdot}Br)^+ &\xrightarrow{\text{Rapid}} Ar{\cdot}Br + H^+ \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad (1)$$

Although the mechanism of the acid-catalysed bromination of organic compounds in water would seem to be established, little is known concerning the mechanism in solvents such as aqueous acetic acid. Recently, however, Derbyshire and Waters (*loc. cit.*) have found that the kinetics of the bromination of benzoic acid in 50% acetic acid points to bromination by the solvated bromine cation, $BrOH_2^+$, and, in some preliminary experiments in 75% acetic acid, Bradfield, Davies, and Long (*J.*, 1949, 1389) obtained approximate bimolecular rate constants for the reaction of hypobromous acid with two phenolic ethers.

In the present study the rates of bromination at 19·8° of a wide range of *p*-substituted and 2:4-disubstituted alkyl phenyl ethers have been determined in 75% acetic acid solution. In all cases the reaction has been found to be of the second order, and satisfactory rate constants have been obtained over 80—90% of the reaction range. (For a preliminary report of the main results see Branch and Brynmor Jones, *Research*, 1952, **5**, 334.) The reaction between *p*-nitrophenetole and hypobromous acid was shown by initial rate measurements to be of the first order with respect to each reactant. Results typical of many are given in Table 1. Attempts to confirm the order of reaction by the "half-life" method proved tedious because of the difficulty of obtaining accurately reproducible concentrations of hypobromous acid. It was found, however, that the ratios

TABLE 1. *Initial rates:* p-*nitrophenetole in* 75% *acetic acid at* 19·8°.

Initial concns. (mole l.$^{-1}$)			
[Ether]	[HOBr]	Initial rate, $10^6 dx/dt$	$(dx/dt)/[Ether][HOBr]$
0·0050	0·00334	5	0·30
0·0100	0·00325	10	0·31
0·0050	0·00643	10	0·31

of the fractional life times in two sets of experiments were very close to the calculated values, as shown in Table 2.

TABLE 2. p-*Nitrophenetole : order of reaction from fractional life periods.*

$[Ether]_1 = 0{\cdot}00500$M; $[HOBr]_1 = 0{\cdot}00334$M					$[Ether]_2 = 0{\cdot}00500$M; $[HOBr]_2 = 0{\cdot}00643$M	
Reaction, %	10	20	30	40	50	60
(t_1/t_2), calc.	1·29	1·26	1·25	1·24	1·23	1·22
(t_1/t_2), obs.	1·30	1·26	1·24	1·24	1·22	1·22

$[Ether]_1 = 0{\cdot}00500$M; $[HOBr]_1 = 0{\cdot}00583$M					$[Ether]_2 = 0{\cdot}00250$M; $[HOBr]_2 = 0{\cdot}00556$M		
Reaction, %	10	20	30	40	50	60	70
(t_1/t_2), calc.	0·98	1·00	1·03	1·07	1·12	1·19	1·27
(t_1/t_2), obs.	0·96	1·00	1·03	1·07	1·11	1·18	1·26

Another complication, which may be overcome by careful choice of experimental conditions, is the instability of hypobromous acid. In 75% acetic acid the most carefully purified specimens decompose slowly to give free bromine, and it was necessary, therefore, to determine the relative reactivities of bromine and hypobromous acid towards aromatic ethers, especially since Derbyshire and Waters had found that at pH 7—8 bromine attacks sodium *p*-anisate about 2000 times as rapidly as does hypobromous acid.

The rate of bromination of *p*-nitroanisole by molecular bromine in 75% acetic acid was expected from earlier halogenation studies to be slow, and it was in fact found to be inappreciable compared with its rate of bromination by hypobromous acid. Because of the formation of HBr_3, and the consequent complexity of the kinetics (Bradfield, Brynmor Jones, and Orton, *J.*, 1929, 2810), the bimolecular coefficient for bromination by bromine falls as the reaction proceeds : nevertheless, the initial value obtained by extrapolation from the present measurements in 75% acetic acid was no greater than 2×10^{-5} l. mole^{-1} sec.$^{-1}$. This value is almost low enough to be accounted for by bromination by HOBr resulting from the hydrolysis of bromine (2), and is in marked contrast to the value 0·162 l. mole^{-1} sec.$^{-1}$ for the bromination of *p*-nitroanisole by hypobromous acid itself.

$$Br_2 + H_2O \rightleftharpoons HOBr + HBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Addition of small amounts of bromide ion to the reaction solution containing pure hypobromous acid leads to the immediate formation of free bromine in accordance with

$$HOBr + Br^- \rightleftharpoons Br_2 + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

equation (3) and rate coefficients, calculated from the initial concentrations of hypobromous acid and aromatic ether, fall rapidly as the reaction proceeds. When, however, the values are re-calculated, with allowance for HOBr removed in this way, satisfactory constants are obtained. These constants agree with those found later when using bromine-free hypobromous acid. This is illustrated by the results given in Table 3.

TABLE 3. p-*Nitrophenetole at* 19·8°.

Initial concn. of aromatic ether, a; initial concn. of HOBr, b_1; concn. of added bromide ion, b_2.

$a = 0{\cdot}00500$M; $b_1 = 0{\cdot}00295$M; $b_2 = 0$. Mean $k_{bl} = 0{\cdot}328$ l. mole^{-1} sec.$^{-1}$.
$a = 0{\cdot}00250$M; $b_1 = 0{\cdot}00359$M; $b_2 = 0{\cdot}00050$M.

Time (sec.)	150	460	920	1310
$\log_{10}[a(b_1 - b_2 - x)/(b_1 - b_2)(a - x)]$	0·0127	0·0393	0·0728	0·1061
k_{bl}	0·330	0·334	0·322	0·316

Addition of chloride ion in an amount greater than that of the hypobromous acid brought the reaction virtually to a standstill, and this, no doubt, may be attributed to the formation of bromine chloride as in equation (4). Although this reagent would be

$$H_2OBr^+ + Cl^- = BrCl + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

expected to be more reactive than free bromine, the fact that no fall in titre was observed during the experiments in 30 min. shows that its brominating power is

extremely low compared with that of hypobromous acid at pH 2. These experiments indicate that hypobromous acid in 75% acetic acid is a much more active brominating agent than bromine, bromine chloride, and the hypobromous acid molecule.

TABLE 4. *Bromination of* p-*nitroanisole: catalysis by mineral acid at* 19·8°.

Concn. of added mineral acid (M)	k_{bi}	$k_{cat.} = (k_{bi} - k_0)/[H_2SO_4]$
—	0·162 (k_0)	—
0·005	0·248	17·2
0·010	0·324	16·2
0·017	0·434	16·0
0·030	0·660	16·6
0·043	0·820	15·8
0·088	1·61	16·5

That the high reactivity of such a solution may be ascribed to the solvated bromine cation is supported by the observation that the reaction of *p*-nitroanisole with hypobromous acid in acetic acid solution is catalysed linearly by mineral acid, the catalytic coefficient remaining almost constant for amounts of added sulphuric acid in the range 0·005—0·090M (see Table 4). It can be calculated from the catalytic coefficient that the rate of reaction in 75% acetic acid corresponds to a hydrogen-ion concentration in this solvent of 0·010 mole $l.^{-1}$. The value calculated from the dissociation constant of acetic acid is 0·015 mole $l.^{-1}$.

It has been suggested by Mauger and Soper (*J.*, 1946, 71) that the brominating agent in acetic acid solution may be the acyl hypobromite. This could be formed by the establishment of either of the following equilibria in acetic acid solutions of HOBr:

$$CH_3{\cdot}CO_2H + HOBr \overset{K_2}{\rightleftharpoons} CH_3{\cdot}CO{\cdot}OBr + H_2O$$

$$CH_3{\cdot}CO{\cdot}O^- + BrOH_2^+ \overset{K_3}{\rightleftharpoons} CH_3{\cdot}CO{\cdot}OBr + H_2O$$

If the hypobromite is formed according to the first equation, and the following reaction ensues, $CH_3{\cdot}CO{\cdot}OBr + ArH \xrightarrow{k_2} CH_3{\cdot}CO_2H + ArBr$, the overall rate of reaction is given by the expression

$$-d[HOBr]/dt = k_2K_2[CH_3{\cdot}CO_2H][HOBr][ArH] \quad . \quad . \quad . \quad . \quad (5)$$

and the observed bimolecular constant by

$$k_{obs.} = k_2K_2[CH_3{\cdot}CO_2H] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

If, on the other hand, the acyl hypobromite results from the second equilibrium, the corresponding relationship becomes

$$-d[HOBr]/dt = k_2K_1K_3K_{HOAc}[CH_3{\cdot}CO_2H][HOBr][ArH] \quad . \quad . \quad . \quad (7)$$

where K_{HOAc} is the dissociation constant of acetic acid, and K_1 is the constant for the equilibrium, $H^+ + HOBr \overset{K_1}{\rightleftharpoons} BrOH_2^+$. In this case

$$k_{obs.} = k_2K_1K_3K_{HOAc}[CH_3{\cdot}CO_2H] \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

For bromination by the solvated cation mechanism the reaction is $BrOH_2^+ + ArH \xrightarrow{k_1} ArBr + H_3O^+$, which leads to the expression

$$k_{obs.} = k_1K_1[H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

To distinguish between the alternative mechanisms of bromination by the solvated bromine cation and by acyl hypobromite, a study was made of the bromination of *p*-nitroanisole in various acetic acid–water mixtures, and the manner in which the rate constant varies with the composition of the medium is shown in Table 5. The shape of the curve obtained by plotting the rate constants against the composition of the medium may be accounted for qualitatively on the basis of bromination by the solvated cation. As acetic acid is added to the aqueous solution the rate increases rapidly from 0·021 to

0·183—a result which arises from the formation of hydrogen ions by the dissociation of the acetic acid. This increase in rate is counteracted, however, by a decrease in the dielectric constant of the medium, as the percentage of acetic acid is increased, so that over quite a range of concentration the observed velocity coefficient remains virtually constant. The rapid decrease in rate which then follows in solutions of high acetic acid content may be

TABLE 5. *Variation in velocity coefficient for the bromination of* p-*nitroanisole with composition of the solvent at* 19·8°.

Weight, %, of acetic acid ...	0	10	25	50	65	75	85
k_{bi}	0·021	0·183	0·194	0·189	0·183	0·162	0·134
			0·190	—	0·175	0·163	0·136

due to two factors. In this region (75—90%), the concentration of acetic acid and of acetic acid monohydrate decreases rapidly, while the concentration curve for the dimer rises steeply (Kipling, *J.*, 1952, 2858). This, combined with the decreasing dielectric constant of the medium, could account for the rapid fall in the rate of bromination observed in 80—90% acetic acid solutions. It is less easy to see how a curve of this form could arise when the acyl hypobromite is the effective brominating agent. Equation (9) may be written in the form

$$k_{obs.} = k_1K_1K_{HOAc}[CH_3{\cdot}CO_2H]/[CH_3{\cdot}CO{\cdot}O^-] \quad . \quad . \quad . \quad . \quad (10)$$

and on comparing this with equations (6) and (8) it is seen that the addition of acetate ion to the reaction solution should lead to a decrease in the bimolecular constant only when bromination occurs by the mechanism of the solvated cation. The figures in Table 6 show that this decrease is observed experimentally. That the fall in the constant is here not

TABLE 6. *Effect of added acetate ion : bromination of* p-*nitroanisole at* 19·8°.

Concn. of added acetate ion (M)	—	0·010	0·050	Satd. soln.
$k_{obs.}$	0·162	0·135	0·122	0·085

as marked as might be expected from equation (10) may be due to an increase in rate in solutions of higher ionic strength, as a result of the operation of a positive secondary salt effect.

An increase in rate in the presence of neutral salts has also been observed (Table 7) and this, presumably, is to be attributed to the same secondary salt effect.

TABLE 7. *Effect of neutral salts on the rate of bromination of* p-*nitroanisole at* 19·8°.

Salt added	Concn. (M)	Observed velocity constant	$\log_{10}(k/k_0)$
—	—	0·162 (k_0)	—
Na_2HPO_4	0·005	0·164	0·005
Na_2SO_4	0·020	0·170	0·021
Li_2SO_4	0·030	0·176	0·036

Direct confirmation that bromination by this mechanism is of predominant importance may be obtained from a study of the catalytic effect of hydrogen ion on the rate of bromination of *p*-nitroanisole in water. If 75% acetic acid is taken to have a pH of 2, the value of the rate constant in 0·015M-aqueous sulphuric acid should be at least as great as in 75% acetic acid containing 0·005M of added mineral acid. Any differences in dielectric constant between the two media would operate to increase further the catalysed rate in water. The values found experimentally were 0·276 l. mole^{-1} sec.$^{-1}$ in acidified aqueous solution, and 0·248 l. mole^{-1} sec.$^{-1}$ in 75% acetic acid containing sulphuric acid.

It would appear, therefore, that the kinetics of the bromination of *p*-nitroanisole and *p*-nitrophenetole by hypobromous acid in 75% acetic acid solution are consistent with bromination by the solvated bromine cation. Catalysis by mineral acid, and the effects of added acetate ion and of neutral salts, indicate that bromination by the acyl hypobromite cannot be of significance under the experimental conditions in this investigation. It is not impossible, however, for the brominating agent in concentrated acetic acid to be the ion, $Br{\cdot}\overset{+}{O}\!<\!\begin{matrix}H\\CO{\cdot}CH_3\end{matrix}$, that is, a bromine ion solvated by an acetic acid molecule. The kinetics of bromination by such an ion would be similar to those by the solvated cation

$BrOH_2^+$, but it is not possible to make a distinction between them on the basis of the present kinetic studies. In 75% acetic acid solution, it is concluded, therefore, that the active brominating agent is either the solvated cation, $BrOH_2^+$, or the brominium ion Br^+.

Experimental

Acetic acid was purified by distillation from 2% chromium trioxide ("AnalaR"), followed by redistillation from 0·2% naphthalene-2-sulphonic acid and the theoretical amount of "AnalaR" acetic anhydride (Orton and Bradfield, *J.*, 1927, 983). Considerable head and tail fractions were rejected, and the final distillate had m. p. 16·4°. This was analysed for excess of acetic anhydride (Orton and Bradfield, *loc. cit.*) and the average content was 0·003 ml. per 100 ml. of purified acid. The reaction medium, containing 75% of acetic acid by weight (n_D^{20} 1·3756), was prepared by adding the calculated volume of acetic acid (after allowance for the slight water content of the purified acid) to a known volume of distilled water.

Hypobromous Acid.—Considerable difficulty was encountered at first in obtaining hypobromous acid sufficiently pure for the kinetic measurements. A few preliminary experiments by Bradfield, Davies, and Long (*loc. cit.*) showed a constant bimolecular coefficient for the bromination of benzyl *p*-nitrophenyl ether by HOBr in 75% acetic acid, whereas their values for *p*-nitrophenetole showed a downward drift. Repetition of these experiments, with carefully purified *p*-nitrophenetole and *p*-nitroanisole, and hypobromous acid prepared by the method of Bradfield, Davies, and Long, confirmed that the rate coefficients decrease as the reaction proceeds. It was suspected, and later confirmed, that this decrease arose from the presence of free bromine in the hypobromous acid. In these experiments the initial titres were, therefore, a measure of total bromine—that due to hypobromous acid and that due to free bromine in solution. The fall in titre during the course of the reaction with the aromatic ether, on the other hand, was a measure of its rate of bromination by hypobromous acid alone. Later an equation was derived which enabled these rate values to be corrected for the presence of free bromine in the HOBr.

If a and b_1 are the initial concentrations of ether and HOBr respectively, and b_2 the concentration of free bromine in solution (the total bromine being $b_1 + b_2 = B$), R_t the observed rate constant after time t, and k the rate constant for bromination by HOBr, then

$$R_t = \frac{1}{t(B-a)} \ln \frac{a(B-x)}{B(a-x)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

and $$R_t(a-x)(B-x) = dx/dt = k(a-x)(b_1-x) \quad . \quad . \quad . \quad . \quad . \quad (12)$$

whence $$R_t = k - kb_2(B-x)^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

Since the values of R_t for substitution in this expression are obtained from equation (11), which is derived by integration of (12) on the assumption that R_t does not vary with t, equation (13) is not strictly valid. It was found, however, that by using the value of x corresponding to $t/2$ so that equation (13) becomes

$$R_t = k - [Kb_2(B-x)_{t/2}^{-1}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

the graph of R_t against $(B-x)_{t/2}^{-1}$ was a straight line of slope $-Kb_2$, and intercept K, for concentrations of bromine not greater than 25% of the concentration of hypobromous acid. Some examples of the results after correction in this way are given in Table 8. These rate constants agree well with the values 0·162 and 0·328 found later, when using purified hypobromous acid.

Table 8.

Ether	Observed rate coefficient, R_t (l. mole^{-1} sec.$^{-1}$) Initial value	Final value	Graphically extrapolated values b_2 (M)	K
p-Nitroanisole	0·120	0·109	0·00021	0·163
p-Nitrophenetole	0·175	0·126	0·00067	0·325
	0·149	0·110	0·00033	0·328

The constancy of the bimolecular coefficients found by Bradfield, Davies, and Long for benzyl *p*-nitrophenyl ether probably arose from a compensation of two opposing factors. It has now been established that with pure, bromine-free hypobromous acid the rate of bromin-

ation of this particular ether increases as the reaction proceeds. For the reasons already given, this increase could be masked if the hypobromous acid contained free bromine, and carefully conducted experiments with hypobromous acid purified by the method given below showed that the constant values found by these earlier workers were in fact fortuitous. The values now obtained are given in Table 9, and it will be seen that the increase in rate persists after the ether had been repeatedly crystallised, and the ratio of ether to hypobromous acid varied five-fold.

TABLE 9. *Bromination of benzyl* p-*nitrophenyl ether by hypobromous acid in* 75% *acetic acid at* 19·8°.

(1) [Ether] = 0·00250 mole/l.; [HOBr] = 0·00644 mole/l.					
Time (sec.)	212	465	850	1320	1540
k (l. mole^{-1} sec.$^{-1}$)	0·114	0·118	0·135	0·184	0·241
Ether recrystallised from ethyl alcohol:					
(2) [Ether] = 0·00250 mole/l.; [HOBr] = 0·00578 mole/l.					
Time (sec.)	215	513	790	1165	
k (l. mole^{-1} sec.$^{-1}$)	0·113	0·121	0·134	0·159	
Ether recrystallised twice from ethyl alcohol and twice from methyl alcohol:					
(3) [Ether] = 0·01250 mole/l.; [HOBr] = 0·00498 mole/l.					
Time (sec.)	200	410	555	825	
k (l. mole^{-1} sec.$^{-1}$)	0·116	0·118	0·123	0·131	

It was suspected that this anomalous behaviour in the case of the benzyl ether arose from the slow formation of free nitrophenol as a result of the debenzylation, and this was in some measure confirmed by qualitative tests, although no derivative of nitrophenol could be isolated.

Pure hypobromous acid was prepared by shaking bromine (3 ml.; " AnalaR "), water (1 l.), and silver sulphate (15 g.) until the heavy precipitate settled, leaving a clear, pale straw-coloured supernatant solution. After filtration, the aqueous solution of hypobromous acid was distilled under reduced pressure (*ca.* 15 mm.) from a water-bath at 40—50°. The all-glass distillation apparatus was coated with a thick layer of black paint to exclude light, and the distillate was collected and stored over carbon tetrachloride in a dark bottle. Only samples of hypobromous acid which had been distilled during the previous 48 hr. were used for kinetic measurements. Traces of bromine were removed from the stored solution as completely as possible by shaking and allowing the carbon tetrachloride to settle. Immediately before each experiment a 25-ml. sample of the aqueous layer was removed and shaken with a further 10 ml. of pure carbon tetrachloride. Solutions of HOBr purified in this way, and diluted to give 75% w/w acetic acid solution, gave no appreciable titre due to bromine during 30 min. at 20°, as shown herewith:

Time (sec.)	0	175	290	580	680	950	1385
HOBr titre, ml.	12·80	—	—	12·80	—	12·80	—
Br_2 titre, ml.	—	0·00	0·00	—	0·00	—	0·02

(Titres in ml. of 0·00500N-sodium thiosulphate for 5-ml. portions of 0·00640 mole/l. HOBr in 75% acetic acid.)

The free bromine was estimated by running the 5-ml. portions of hypobromous acid solution into an excess of benzoic acid in 75% acetic acid to remove the HOBr, adding potassium iodide, and titrating the liberated iodine against the thiosulphate. The total hypobromous acid and bromine was estimated by direct titration against standard thiosulphate in the usual way.

Kinetic Measurements.—All measurements were made at 19·8° ± 0·02°. Because of the high reactivity of hypobromous acid towards the aromatic ethers it was essential to reduce the time taken to mix the solutions, and thereby minimise errors in timing. For this, a special reaction vessel was made consisting of two small long-necked flasks with ground glass stoppers, and connected in such a way as to form an H-shaped vessel with bulbs at both feet. The reactants were introduced into separate limbs, and the reaction initiated by inverting and rapidly shaking the vessel. The progress of the reaction was followed by running 5-ml. samples into aqueous potassium iodide, containing a little solid carbon dioxide to reduce the oxidation of the liberated hydrogen iodide during the determination. The liberated iodine was titrated against 0·005N-sodium thiosulphate. Individual values of the bimolecular coefficient in any experiment usually varied over approximately 3%, but the mean values obtained in different

experiments were usually within 2% of one another. The following values for *p*-nitroanisole are typical.

(1) p-*Nitroanisole in* 75% *acetic acid at* 19·8°.

[Ether] = 0·00500 mole/l.; [HOBr] = 0·00633 mole/l.

Time (sec.)	0	240	494	750	1024
Titre, ml.	25·55	21·46	18·46	16·45	14·73
10^3x (mole/l.)		1·01	1·75	2·26	2·68
k_{bl} (l. mole^{-1} sec.$^{-1}$)		0·163	0·164	0·160	0·160

(2) p-*Nitroanisole in* 75% *acetic acid with* 0·088M-H_2SO_4.

[Ether] = 0·00500 mole/l.; [HOBr] = 0·00182 mole/l.

Time (sec.)	46	75	115	205
10^3x (mole/l.)	0·54	0·76	1·02	1·36
k_{bl} (l. mole^{-1} sec.$^{-1}$)	1·64	1·58	1·63	1·63

p-Nitroanisole, m. p. 53°, *p*-nitrophenetole, m. p. 59°, and benzyl *p*-nitrophenyl ether, m. p. 106°, were prepared by standard methods and purified by repeated crystallisation from absolute alcohol.

Grateful acknowledgment is made to the Distillers Co. Ltd. and to Imperial Chemical Industries Limited for grants to the Department. One of the authors is also indebted to the Department of Scientific and Industrial Research and to the Worsfield Trustees for maintenance grants.

UNIVERSITY COLLEGE, HULL. [*Received, December 23rd,* 1953.]

Thermochemistry of Organo-boron Compounds. Part IV. Dimethylaminochloroborines.*

By H. A. SKINNER and N. B. SMITH.

[Reprint Order No. 5078.]

Values are reported for the heat of hydrolysis of dimethylaminodichloroborine, and for the heat of hydrolysis in hydrochloric acid of bisdimethylaminochloroborine. From these data, the heats of formation of the compounds in the liquid state are derived, *viz.*:

$$\Delta Hf^\circ[B(NMe_2)Cl_2,liq.] = -108{\cdot}0 \pm 1{\cdot}5 \text{ kcal./mole}$$

and $$\Delta Hf^\circ[B(NMe_2)_2Cl,liq.] = -95{\cdot}2_5 \pm 1{\cdot}5 \text{ kcal./mole}$$

In the group of compounds $B(NMe_2)_nCl_{3-n}$ ($n = 0, 1, 2, 3$), for which thermal data are now complete, the bond energy term values $\bar{D}$(B–Cl) and $\bar{D}$(B–NMe_2) are not constant throughout the group. It is shown that the $B(NMe_2)Cl_2$ molecule is more stable by 12·1 kcal./mole, and the $B(NMe_2)_2Cl$ molecule more stable by 8·9 kcal./mole, than would be the case if the B–Cl and B–NMe_2 bonds in these molecules had the same energy as in BCl_3 and $B(NMe_2)_3$.

An explanation of the enhanced bond-energy term values in the mixed molecules is given by a molecular-orbital treatment of back-co-ordination in this group of molecules. Agreement with the experimental results is obtained if it is assumed that back-co-ordination is more powerful from nitrogen to boron than it is from chlorine to boron. The nitrogen atom would seem to be of the order of three times as effective as the chlorine atom in this respect.

WIBERG and SCHUSTER (*Z. anorg. Chem.*, 1933, **213**, 94) have described the properties of the compounds $B(NMe_2)_nCl_{3-n}$ ($n = 1, 2, 3$), obtained from the reaction under controlled conditions of dimethylamine with boron trichloride. In Part III * we reported on the heat of hydrolysis in hydrochloric acid of one of these compounds, trisdimethylaminoborine, $B(NMe_2)_3$. We have also (Skinner and Smith, *Trans. Faraday Soc.*, 1953, **49**, 601) re-measured

* Part III, Skinner and Smith, *J.*, 1953, 4025.

the heat of hydrolysis of boron trichloride. The present paper deals with the heats of hydrolysis of the two intervening compounds in the series, bisdimethylaminochloroborine, $B(NMe_2)_2Cl$, and dimethylaminodichloroborine, $B(NMe_2)Cl_2$. Series of this type are of interest in that they provide group data, which can be examined in terms of simple additivity postulates; in the present case we find that the bond-energy terms of the B–Cl and B–NMe_2 linkages are not additive in the group $B(NMe_2)_nCl_{3-n}$ ($n = 0, 1, 2$ 3) and that the deviations from additivity are appreciable.

Experimental

Preparation of Compounds.—Dimethylaminodichloroborine was prepared by Brown's method (*J. Amer. Chem. Soc.*, 1952, **74**, 1219), interaction of equivalent quantities of boron trichloride and dimethylamine in dry benzene, followed by addition of triethylamine (which is precipitated as the base hydrochloride, NEt_3,HCl, on standing). After filtration from the solid products, the benzene was separated by distillation through a Fenske column. The high-boiling residue was transferred to a smaller distillation unit and fractionated in nitrogen at reduced pressure through a 6″ steel-gauze packed column; the fraction, b. p. 52—54°/92 mm., was retained. This was further distilled in a high vacuum, and the purified sample stored at −80°. Brown and Osthoff (*ibid.*, p. 2340) have reported that the dimerisation of dimethylaminodichloroborine, which occurs easily at room temperature, is considerably suppressed if the monomer is stored *in vacuo* at low temperatures.

Bisdimethylaminochloroborine was prepared by an extension of Brown's method (*loc. cit.*). A solution of dimethylaminodichloroborine in benzene was prepared, as described above, and this was then treated with a second equivalent of dimethylamine, followed by a further addition of triethylamine. After standing, solid products were filtered off, and the clear solution was distilled through a Fenske column at atmospheric pressure. The fraction, b. p. 145—148°, was collected and redistilled under reduced pressure in the small distillation unit; the sample, b. p. 50—52°/21 mm., was retained. This was further distilled *in vacuo*, and small samples were collected and sealed in thin, weighed, glass ampoules.

Calorimeter.—The calorimeter was described by Skinner and Smith (*loc. cit.*). The hydrolysis studies were carried out by breaking ampoules of the reactants under the surface either of 500 ml. of water or of 500 ml. of N-hydrochloric acid contained in the Dewar vessel, and following the ensuing temperature changes through the resistance changes of a shielded thermistor element immersed in the solution. The experiments were done at 25°.

Units.—The calorimeter was calibrated electrically. Heat quantities are given in thermochemical calories, 1 cal. = 4·1840 abs. joules.

Results.—(1) *Dimethylaminodichloroborine.* This substance is hydrolysed extremely rapidly at 25°, and the reaction may take place with explosive violence. Capillary side-arm ampoules—such as we have used successfully to moderate the violence of the hydrolysis of boron trichloride—were not always satisfactory in the present case, and several Dewar reaction vessels were shattered as a result. Ultimately, the method adopted was to dilute the dimethylaminodichloroborine; the ampoules were part-filled with reactant, to which approximately twice as much carbon tetrachloride (by volume) was then added as diluent. When these ampoules were broken, hydrolysis occurred rapidly, but non-explosively.

The observed heats of hydrolysis, $\Delta H_{obs.}$, refer to the reaction system

$$B(NMe_2)Cl_2(liq./CCl_4) + (n + 3)H_2O(liq.) \longrightarrow (H_3BO_3 + NH_2Me_2Cl + HCl),nH_2O \quad . \quad (1)$$

and are related to the heat of formation of liquid dimethylaminodichloroborine by the thermochemical equation

$$\Delta Hf^\circ[B(NMe_2)Cl_2,liq.] = \Delta Hf^\circ(H_3BO_3 + NH_2Me_2Cl + HCl),nH_2O - 3\Delta Hf^\circ(H_2O,liq.) - \Delta H_{obs.} \quad . \quad . \quad (2)$$

In using * eqn. (2), thermal data from the following sources were assumed: $\Delta Hf^\circ(HCl,nH_2O)$ and $\Delta Hf^\circ(NH_2Me_2Cl,nH_2O)$ from "Selected Values of Chemical Thermodynamic Properties," Nat. Bur. Stand., Washington, Circular No. 500; $\Delta Hf^\circ(H_2O,liq.) = -68{\cdot}317$ kcal./mole (N.B.S. tables); $\Delta Hf^\circ(H_3BO_3,nH_2O)$ from Prosen, Johnson, and Pergiel (Nat. Bur. Stand., Report No. 1552, 1953).

* The heat of mixing of $B(NMe_2)Cl_2$(liq.) with CCl_4(liq.) was measured independently, and found to be negligible. The heat of mixing of the products was also found to be negligible.

A selected group of the results obtained is given in Table 1.

TABLE 1. *Heat of hydrolysis of* $B(NMe_2)Cl_2$.

Expt.	$B(NMe_2)Cl_2$ (moles)	n	$-\Delta H_{obs.}$ (kcal.)	$\Delta Hf°[B(NMe_2)Cl_2]$ (kcal./mole)	Mean values (kcal./mole)
1	0·00670	4146	54·9	−108·2	
2	0·00622	4466	55·0	−108·1	$-\Delta H_{obs.} = 55·1$
3	0·00781	3556	55·7	−107·4	$\Delta Hf° = -108·0$
4	0·00702	3957	54·8	−108·5	
5	0·00538	5164	55·2	−108·0	

Estimation of the moles of reactant used in each experiment was made by volumetric analysis of the hydrolysis products for (*a*) total chlorine-ion content, and (*b*) free hydrochloric acid. These analyses generally agreed with each other within 1%, establishing the purity of the dimethylaminodichloroborine at >99%. The overall error of the thermochemical study—with allowance of an error of 1% in analysis, and an error of similar order in the calorimetry—is estimated at ±1 kcal./mole. The overall error in $\Delta Hf°$ includes the errors that may rest in the subsidiary thermochemical data required in eqn. (2), and amounts to ±1·5 kcal./mole.

(2) *Bisdimethylaminochloroborine.* This substance is hydrolysed with moderate speed in water, and rapidly in N-hydrochloric acid. The acid hydrolysis has advantages from the thermochemical standpoint, in that the free dimethylamine produced on hydrolysis is completely held in solution as the salt, NH_2Me_2Cl. The experiments were performed by breaking weighed ampoules directly into 500 ml. of N-hydrochloric acid:

$$B(NMe_2)_2Cl(liq.) + 3H_2O(liq.) + (n+1)HCl(54H_2O) \longrightarrow (H_3BO_3 + 2NH_2Me_2Cl,27H_2O),nHCl(54H_2O) \quad . \quad . \quad (3)$$

where the excess of hydrochloric acid is denoted by n. The values of $\Delta Hf°[B(NMe_2)_2Cl,liq.]$ were derived from the thermochemical equation corresponding to eqn. (3), *viz.*,

$$\Delta Hf°[B(NMe_2)_2Cl,liq.] = \Delta Hf°[H_3BO_3,54(n+1)H_2O] + 2\Delta Hf°[NH_2Me_2Cl,27(n+1)H_2O] - 3\Delta Hf°(H_2O,liq.) - \Delta Hf°(HCl,54H_2O) - \Delta H_{obs.} \quad . \quad . \quad . \quad . \quad (4)\ *$$

A selection from the results obtained is given in Table 2.

TABLE 2. *Acid hydrolysis of* $B(NMe_2)_2Cl$.

Expt.	$B(NMe_2)_2Cl$ (moles)	n	$-\Delta H_{obs.}$ (kcal.)	$\Delta Hf°[B(NMe_2)_2Cl]$ (kcal./mole)	Mean values
1	0·004857	102	59·0	−95·3	
2	0·005179	95	59·15	−95·2	$-\Delta H_{obs.} = 59·1$ kcal.
3	0·004978	99	58·95	−95·4	$\Delta Hf° = -95·25$ kcal./mole
4	0·004651	106	59·25	−95·1	

The moles of reactant used in each experiment were calculated from the weight of the sample; analyses were not made on the calorimeter contents after each run. Analyses, both of chlorine ion and of dimethylamine content, were made on chosen samples from the stock of bisdimethylaminochloroborine, which generally agreed with one another satisfactorily, indicating purity † of 99—100% of the reactant. The overall error in $\Delta H_{obs.}$ is estimated at ±1 kcal./mole.

DISCUSSION

Table 3 lists the values we have obtained for the heats of formation of each member of the group $B(NMe_2)_nCl_{3-n}$. The latent heats of vaporisation ($\Delta H_{vap.}$) are from data by Wiberg and Schuster (*loc. cit.*), Burg and Randolph (*J. Amer. Chem. Soc.*, 1951, **73**, 953), and the N.B.S. tables (Circular 500).

* Eqn. (4) neglects the heats of mixing of the products of reaction (3), which are small at the dilutions employed.

† It is possible that bisdimethylaminochloroborine disproportionates in the sense $2B(NMe_2)_2Cl \longrightarrow B(NMe_2)Cl_2 + B(NMe_2)_3$. Analysis of hydrolysis products would not reveal such disproportionation, but no evidence was found of dimer formation $[B(NMe_2)Cl_2]_2$, even on long standing.

From the $\Delta Hf°$(g.) values in Table 3, we may calculate the heats of the two following redistribution reactions,* *viz.*,

(*a*) $\frac{2}{3}BCl_3(g.) + \frac{1}{3}B(NMe_2)_3(g.) \longrightarrow B(NMe_2)Cl_2(g.)$ $\Delta H = -12{\cdot}1(\pm 1{\cdot}4)$ kcal./mole

and

(*b*) $\frac{1}{3}BCl_3(g.) + \frac{2}{3}B(NMe_2)_3(g.) \longrightarrow B(NMe_2)_2Cl(g.)$ $\Delta H = -8{\cdot}9(\pm 1{\cdot}6)$ kcal./mole

According to the postulate of constant transferable bond energy term values, redistribution reactions such as (*a*) and (*b*) should be thermoneutral (cf. Mortimer and Skinner, *J.*, 1953, 3189; Skinner and Tees, *J.*, 1953, 3378). The data show that the bond-energy terms $\bar{D}$(B–Cl) and $\bar{D}$(B–NMe_2) are *not* constant in the group $B(NMe_2)_nCl_{3-n}$, and that there is an overall enhancement in the bond-energy term values of 12·1 kcal./mole in dimethylaminodichloroborine, and of 8·9 kcal./mole in bisdimethylaminochloroborine. Alternatively expressed, the dimethylaminodichloroborine molecule is more stable by 12·1 kcal./mole than would be the case if the B–Cl bonds should have the same mean energy as in boron trichloride, and the B–NMe_2 bond the same energy as in trisdimethylaminoborine; correspondingly, the bisdimethylaminochloroborine stability is enhanced by 8·9 kcal./mole over the value calculated in like manner.

TABLE 3.

Compound	$\Delta Hf°$(liq.)	$\Delta H_{vap.}$	$\Delta Hf°$(g.)
BCl_3	$-103{\cdot}0 \pm 1$	5·5	$-97{\cdot}5 \pm 1$
BCl_2NMe_2	$-108{\cdot}0 \pm 1{\cdot}5$	$8{\cdot}9 \pm 0{\cdot}3$	$-99{\cdot}1 \pm 1{\cdot}8$
$BCl(NMe_2)_2$	$-95{\cdot}2_5 \pm 1{\cdot}5$	$10{\cdot}0 \pm 0{\cdot}5$	$-85{\cdot}3 \pm 2$
$B(NMe_2)_3$	$-77{\cdot}1 \pm 1$	$11{\cdot}2 \pm 0{\cdot}2$	$-65{\cdot}9 \pm 1{\cdot}2$

We have sought an explanation of these results by applying a simple molecular-orbital treatment of π-bonding (" back-co-ordination ") to this group of molecules. It is generally accepted that in molecules of type BX_3 (X = halogen, NR_2, OR) there is some measure of π-bonding (occasioned by the existence of a vacant $2p_z$ orbital on the boron atom) which is superimposed on the trigonal B–X σ-bonding. Little is known, however, of the relative importance of such π-bonding in different BX_3 systems. We find that the pattern of the present set of results is satisfactorily reproduced if we assume that back-co-ordination from nitrogen to boron is more powerful than from chlorine to boron.

The problem is one of six electrons, extending over four atoms in a plane. The localised reference system is considered to have the $2p_z$ boron orbital vacant, and to have p_z^2 pairs localised on each nitrogen and/or chlorine atom; we are interested in the energy stabilisation resulting from the delocalisation of the three pairs (p_z^2) of electrons. The procedure may be illustrated by the particular case of $B(NMe_2)Cl_2$, for which the secular determinant is shown below:

$$\begin{vmatrix} \alpha_B - \varepsilon & \gamma^* - S^*\varepsilon & \gamma - S\varepsilon & \gamma - S\varepsilon \\ \gamma^* - S^*\varepsilon & \alpha_N - \varepsilon & 0 & 0 \\ \gamma - S\varepsilon & 0 & \alpha_{Cl} - \varepsilon & 0 \\ \gamma - S\varepsilon & 0 & 0 & \alpha_{Cl} - \varepsilon \end{vmatrix} = 0 \quad . \quad . \quad . \quad . \quad . \quad (5)$$

α_B, α_N, and α_{Cl} are coulomb integrals, γ and γ^* are exchange integrals, and S^* and S are overlap integrals (cf. Roothaan and Mulliken, *J. Chem. Physics*, 1948, **16**, 118; γ and S refer to B–N bonds, γ^* and S^* to B–Cl bonds). Solution of eqn. (5) yields the energy levels, and the total electronic energy of the delocalised system is obtained by filling the lowest three of these. The energy stabilisation, relative to the localised reference system, is symbolised by $R_\pi(BNCl_2)$ and is given by $2[\sum_{i=1}^{3} \varepsilon_i - 2\alpha_{Cl} - \alpha_N]$.

Eqn. (5) (and the similar equations relating to the systems BN_2Cl, BN_3, and BCl_3) may be simplified by assuming $\alpha_{Cl} = \alpha_N$—a reasonable approximation in view of the

* The limits of error quoted are standard deviations. It should be noted that part of the error (*ca.* ±0·5 kcal./mole) included in the $\Delta Hf°$(g.) values of Table 3 arises from uncertainties in *assumed* thermochemical data, *e.g.*, in $\Delta Hf°(H_3BO_3)$; since this source of error occurs with the same sign on both sides of the redistribution reactions (*a*) and (*b*) it is not relevant to the calculation of the probable error in the ΔH values.

equal electronegativities of N and Cl. By making the substitutions, $(\gamma - S\alpha_{Cl}) = \beta$, $(\gamma^* - S^*\alpha_{Cl}) = \beta^*$, $(\alpha_N - \alpha_B) = (\alpha_{Cl} - \alpha_B) = \delta = m\beta^*$, and $\beta = n\beta^*$, the set of equations (6) is obtained :

$$\left.\begin{aligned}
R_\pi(BCl_3) &= \beta^*(1 - 3S^2)^{-1}\{(m + 6nS) - (m^2 + 12n^2 + 12nmS)^{\frac{1}{2}}\} \\
R_\pi(BNCl_2) &= \beta^*(1 - 2S^2 - S^{*2})^{-1}\{(m + 4nS + 2S^*) - [m^2 + 4(1 + 2n^2) \\
&\qquad + 4m(S^* + 2nS) - 8(nS^* - S)^2]^{\frac{1}{2}}\} \\
R_\pi(BN_2Cl) &= \beta^*(1 - S^2 - 2S^{*2})^{-1}\{(m + 2nS + 4S^*) - [m^2 + 4(2 + n^2) \\
&\qquad + 4m(2S^* + nS) - 8(nS^* - S)^2]^{\frac{1}{2}}\} \\
R_\pi(BN_3) &= \beta^*(1 - 3S^{*2})^{-1}\{(m + 6S^*) - (m^2 + 12 + 12mS^*)^{\frac{1}{2}}\}
\end{aligned}\right\} \quad (6)$$

A further assumption included in eqns. (6) is that the overlap integrals S(B–Cl) and S^*(B–N) remain constant throughout the series $BCl_3 \longrightarrow BN_3$.

Values of R_π (in units of β^*) are given in Table 4 for a range of values of the unknown parameters m and n. The overlap integrals S and S^* were calculated from the formulæ

TABLE 4. *R_π Values in units of β^*.*

n =	1·5	0·9	0·7	0·5	0·3	
$R_\pi(BCl_3)$	3·486	1·956	1·466	0·973	0·496	
$R_\pi(BNCl_2)$	3·119	2·042	1·743	1·499	1·336	$m = 0·5$
$R_\pi(BN_2Cl)$	2·692	2·113	1·977	1·879	1·826	
$R_\pi(BN_3)$	2·181	2·181	2·181	2·181	2·181	
$R_\pi(BCl_3)$	3·194	1·702	1·225	0·767	0·354	
$R_\pi(BNCl_2)$	2·822	1·775	1·487	1·253	1·092	$m = 1·0$
$R_\pi(BN_2Cl)$	2·406	1·845	1·714	1·617	1·561	
$R_\pi(BN_3)$	1·913	1·913	1·913	1·913	1·913	
$R_\pi(BCl_3)$	2·918	1·490	1·043	0·627	0·272	
$R_\pi(BNCl_2)$	2·566	1·560	1·287	1·066	0·914	$m = 1·5$
$R_\pi(BN_2Cl)$	2·163	1·628	1·502	1·410	1·353	
$R_\pi(BN_3)$	1·694	1·694	1·694	1·694	1·694	

given by Mulliken, Rieke, Orloff, and Orloff (*J. Chem. Physics*, 1949, **17**, 1248) assuming * the bond distances $r_{B-N} = 1·44$ Å ($S^* = 0·22$), and $r_{B-Cl} = 1·73$ Å ($S = 0·206$).

Table 5 gives values of two quantities, Δ_1 and Δ_2, defined in eqn. (7) :

$$\begin{aligned}
\Delta_1 &= R_\pi(BNCl_2) - \tfrac{2}{3}R_\pi(BCl_3) - \tfrac{1}{3}R_\pi(BN_3) \\
\Delta_2 &= R_\pi(BN_2Cl) - \tfrac{1}{3}R_\pi(BCl_3) - \tfrac{2}{3}R_\pi(BN_3) \quad . \quad . \quad . \quad . \quad . \quad (7)
\end{aligned}$$

The entries under Δ_1 and Δ_2 in Table 5 are all of the form $x\beta^*$, where x is a positive number. The implication is that an *enhancement* of the bond-energy terms in the mixed molecules

TABLE 5. *Δ Values in units of β^*.*

		n = 1·5	0·9	0·7	0·5	0·3
$m = 0·5$	Δ_1	0·068	0·011	0·038	0·123	0·278
	Δ_2	0·076	0·008	0·035	0·100	0·206
$m = 1·0$	Δ_1	0·055	0·003	0·033	0·104	0·219
	Δ_2	0·067	0·0025	0·030	0·086	0·168
$m = 1·5$	Δ_1	0·056	0·0025	0·027	0·083	0·168
	Δ_2	0·061	0·002	0·025	0·072	0·133

$BNCl_2$ and BN_2Cl is predicted over the complete range given to the parameters m and n. But whereas $\Delta_1 > \Delta_2$ in case $n < 1$, the reverse is calculated for the case $n > 1$.

Experimentally, we find the enhancement larger † in $B(NMe_2)Cl_2$ than in $B(NMe_2)_2Cl$,

* The distance r_{B-Cl} in BCl_3 is given by electron-diffraction studies; r_{B-N} is not known in this series of compounds. The value chosen is based on the measured values in borazole and crystalline boron nitride.

† From the experimental values $\Delta_1 = 12·1 \pm 1·4$ kcal./mole and $\Delta_2 = 8·9 \pm 1·8$ kcal./mole, we have $(\Delta_1 - \Delta_2) = 3·2 \pm 2·1$ kcal./mole (the quoted error is the standard deviation). The magnitude of the possible error in the value $(\Delta_1 - \Delta_2) = 3·2$ kcal./mole is unfortunately too large to allow very definite conclusions to be drawn, and this point should be borne in mind in the ensuing discussion.

corresponding to $\Delta_1 > \Delta_2$, and $n < 1$. Moreover, it would seem that n is required to be appreciably less than unity; thus, *e.g.*, if we accept the values $m = 0{\cdot}5$, $n = 0{\cdot}3$, and $\beta^* = -43{\cdot}5$ kcal./mole, the calculated values are $\Delta_1 = 12{\cdot}1$ kcal. and $\Delta_2 = 8{\cdot}96$ kcal., in excellent agreement with the experimental values (12·1 and 8·9 respectively). This particular choice of parameter values represents only one among many that would fit the experimental data satisfactorily; the important point is that, if m is chosen $>0{\cdot}5$, the trend is for n to become $<0{\cdot}3$ if agreement with experiment is to be retained.

Values of n of the order 0·3 or less imply that the exchange integral γ^* is some three or more times larger than γ. The physical interpretation of this is that back-co-ordination from the nitrogen $2p_z^2$ electrons to boron is at least thrice as effective as from the $3p_z^2$ electron pair * in chlorine. On the other hand, the overlap integrals S^* and S are almost the same for the internuclear separations we have used. This suggests that a general proportionality between exchange and overlap integrals, $kS \sim \gamma$, does not obtain. A more limited relation, $k_{nn'}S \sim \gamma$, in which the proportionality constants depend upon the principal quantum numbers n, n' of the interacting electrons, may be more satisfactory as an approximation.

Effective back-co-ordination in a given BX_3 molecule will compensate internally the electron deficiency of the $2p_z$ orbital of trigonal boron. In this sense, one might expect that BX_3 molecules which show comparatively weak acceptor behaviour are highly compensated internally. The present results confirm this, boron trichloride (small γ) being an active acceptor molecule, and trisdimethylaminoborine (large γ) a relatively weak acceptor. On this basis we might expect a large value for γ(B–O) in the alkyl borates (weak acceptor properties), and a similar trend in the values Δ_1, Δ_2 for the molecules $B(OR)Cl_2$, $B(OR)_2Cl$, to those found here. Studies on these latter compounds are in progress.

The authors thank Professor G. Gee, F.R.S., for his interest in this work, and Professor G. E. Coates for advice on the preparation of the dimethylaminochloroborines.

CHEMISTRY DEPARTMENT, UNIVERSITY OF MANCHESTER. [*Received, January 30th*, 1954.]

Polynuclear Heterocyclic Systems. Part VIII.† *Synthetic Applications of the Schmidt Reaction.*

By G. M. BADGER and J. H. SEIDLER.

[Reprint Order No. 5125.]

Although the Beckmann transformation of the chrysenequinone monoxime (V) leads to the two amido-acids (II and VI), the Schmidt reaction with chrysenequinone gives the amido-acid (II) exclusively. By treatment with hydrazoic acid the two amido-acids have been converted into 1 : 2- (III) and 7 : 8-benzophenanthridone (VII) respectively, and thence into the benzophenanthridines.

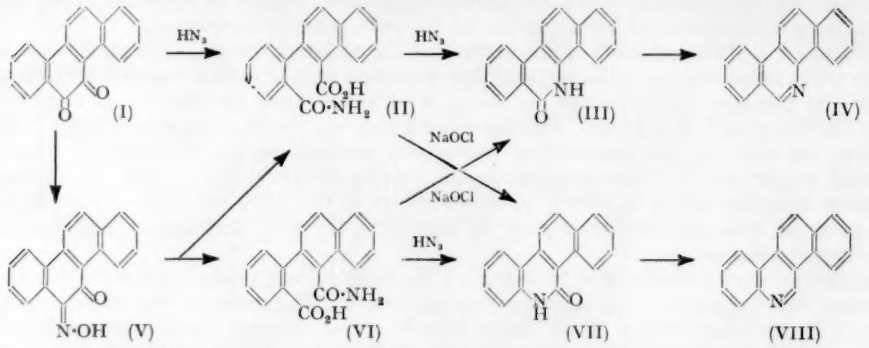
PHENANTHRIDONE has been prepared by the action of hydrazoic acid on phenanthraquinone (Caronna, *Gazzetta*, 1941, **71**, 481), but the general reaction has not been investigated in detail and little information exists which would enable one to predict the result for an unsymmetrical *o*-quinone (cf. Stephenson, *J.*, 1949, 2620; Badger, Howard, and Simons, *J.*, 1952, 2849).

Caronna (*loc. cit.*) found that treatment of the chrysenequinone (I) with excess of hydrazoic acid gave 1 : 2-benzophenanthridone (III) exclusively. This has now been confirmed, and it has also been shown that if only 1 mol. of hydrazoic acid is used, the amido-acid (II) is obtained, which on further treatment with hydrazoic acid yields 1 : 2-benzophenanthridone.

* The symbols $2p_z^2$, $3p_z^2$ beg the question as to the proper description of the lone-pair donor electrons on the N and Cl atoms.

† Part VII, *J.*, 1953, 2774.

On the other hand, Beckmann rearrangement of the chrysenequinone mono-oxime (probably V) has been shown (Graebe, *Annalen*, 1904, **335**, 122) to lead to the two amido-acids (II and VI). The acid (II) gives 1 : 2-benzophenanthridone (III) on treatment with hydrazoic acid (cf. above), and, as Graebe (*loc. cit.*) has shown, it gives 7 : 8-benzophenanthridone (VII) on treatment with sodium hypochlorite. Similarly, the acid (VI) has

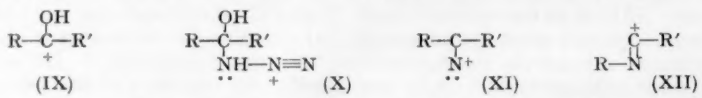


now been shown to give 7 : 8-benzophenanthridone (VII) with hydrazoic acid; and as Graebe (*loc. cit.*) has shown it gives 1 : 2-benzophenanthridone with sodium hypochlorite.

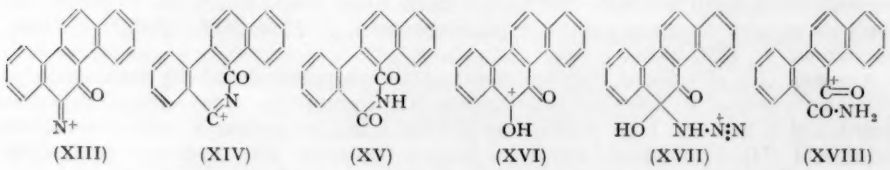
In each case the benzophenanthridones (III, VII) were converted into the chlorobenzophenanthridines, which were then reduced to the benzophenanthridines (IV and VIII). The same bases were obtained from the phenanthridones by reduction with lithium aluminium hydride, followed by dehydrogenation of the unstable dihydrides. The structures of these benzophenanthridines follow from the independent syntheses of the 1 : 2-benzo-compound by Kenner, Ritchie, and Statham (*J.*, 1937, 1169) and by Ritchie (*J. Proc. Roy. Soc. N.S.W.*, 1946, **78**, 173).

The absorption spectra (Figure) of both benzophenanthridines resembled that of chrysene very closely, except that the group III absorption bands are much more intense in the aza-hydrocarbons.

The mechanism of the Schmidt reaction with ketones seems to be fairly well established (Smith *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 320; 1950, **72**, 2503, 3718; Newman and Gildenhorn, *ibid.*, 1948, **70**, 317). The ketone is converted into the carbonium ion (IX) which with hydrazoic acid gives (X). Elimination of water and of nitrogen then gives the intermediate ion (XI) which immediately rearranges to the carbonium ion (XII). On the addition of water, this gives the amide. The Beckmann transformation of



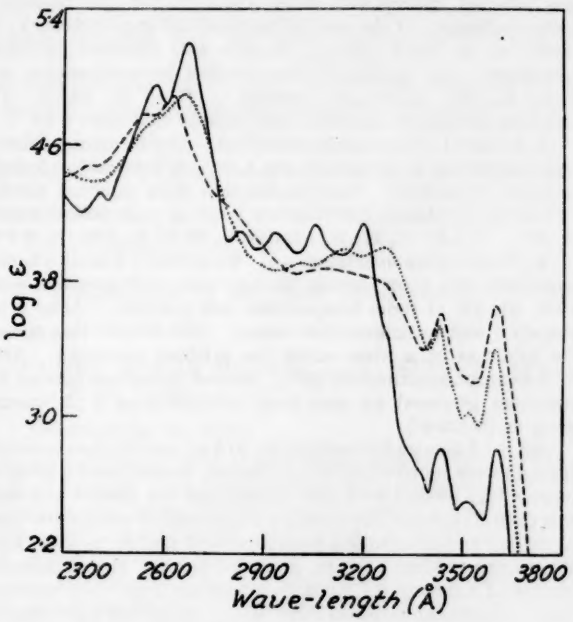
ketoximes is believed to be essentially similar, both reactions proceeding *via* the ion (XI). The Schmidt reaction with *o*-quinones, and the Beckmann transformation of quinone oximes are not so well understood. With chrysenequinone (I) the Schmidt reaction gives



the amido-acid (II) and thence 1 : 2-benzophenanthridone (III) exclusively, but the Beckmann transformation of chrysenequinone oxime (V) yields both amido-acids. It is suggested that the Beckmann transformation proceeds normally to give the ion (XIII)

which subsequently rearranges to the carbonium ion (XIV). Addition of 1 mol. of water would give the imide (XV), but addition of 2 mols. of water would give a mixture of both amido-acids.

On the other hand, as only one product is obtained in the Schmidt reaction with chrysenequinone it seems that the ion (XIII) is not then formed. The carbonium ion (XVI) is probably first formed, and this would react with hydrazoic acid to give (XVII). Subsequent elimination of nitrogen evidently leads to fission of the carbon–carbon bond



Ultra-violet absorption spectra of chrysene (———) and 1 : 2-(— —) and 7 : 8-benzophenanthridine (. . . .), all in ethanol.

and formation of the ion (XVIII). The latter would lead to the amido-acid (II) on addition of water, or to 1 : 2-benzophenanthridone (III) on treatment with a further mol. of hydrazoic acid.

Experimental

2-o-*Benzamido*-1-*naphthoic Acid*.—A mechanically stirred solution of chrysenequinone (6 g.) in concentrated sulphuric acid (20 c.c.) was treated with sodium azide (1·7 g.) at such a rate that the temperature was maintained at 50° (40 min.). After a further 30 min. at 50°, the mixture was poured into water (300 c.c.). The precipitate was collected, washed with water, and freed from unchanged chrysenequinone and some 1 : 2-benzophenanthridone by treatment with 10% sodium carbonate solution. After acidification with hydrochloric acid, the product was collected (70% yield). Recrystallisation from alcohol gave 2-*o*-benzamido-1-naphthoic acid as colourless plates, m. p. 230° (Found : C, 74·3; H, 4·4; N, 4·5. Calc. for $C_{18}H_{13}O_3N$: C, 74·2; H, 4·5; N, 4·8%).

The same acid, m. p. 230°, was obtained together with 2-*o*-carboxyphenyl-1-naphthoamide, m. p. 275°, from chrysenequinone mono-oxime by the Beckmann rearrangement according to Graebe (*loc. cit.*) who gave m. p. 220° and 275° respectively.

1 : 2-*Benzophenanthridone*.—Powdered sodium azide (1 g.) was added gradually to a well-stirred solution of the above benzamidonaphthoic acid (3 g.) in concentrated sulphuric acid (15 c.c.) at 55—60°. The mixture was kept at 55—60° for a further hour, and then poured into water. The product was freed from unchanged acid by treatment with 10% sodium carbonate solution and washed with water. After one recrystallisation from glacial acetic acid the 1 : 2-benzophenanthridone was obtained as colourless prisms, m. p. 330°.

The same benzophenanthridone was obtained in almost quantitative yield by the addition

of powdered sodium azide (3·5 g.) to chrysenequinone (6 g.) in concentrated sulphuric acid (20 c.c.) (cf. Caronna, *loc. cit.*). After crystallisation from glacial acetic acid and sublimation in a high vacuum 1 : 2-benzophenanthridone had m. p. 332° (Graebe, *loc. cit.*, gives m. p. 332·5°).

In agreement with Graebe, 1 : 2-benzophenanthridone was also obtained from 2-*o*-carboxyphenyl-1-naphthoamide by oxidation with sodium hypochlorite.

9-*Chloro*-1 : 2-*benzophenanthridine*.—1 : 2-Benzophenanthridone (2 g.), phosphorus oxychloride (18 c.c.), and dimethylaniline (0·6 c.c.) were refluxed for 4 hr. The excess of phosphorus oxychloride was then removed *in vacuo*, and the residue treated with iced water. The product was collected, washed with water, and extracted with benzene, and the solution was evaporated. Recrystallisation of the residue from alcohol gave 2-*chloro*-1 : 2-*benzophenanthridine* as colourless plates, m. p. 156·5° (90%). It was also obtained as colourless blades from benzene–light petroleum. For analysis it was purified by sublimation at 120°/5 × 10^{-5} mm. (Found : C, 77·5; H, 3·8. $C_{17}H_{10}NCl$ requires C, 77·4; H, 3·8%). It was recovered unchanged from refluxing alcohol or alcoholic hydrochloric acid after 2 hr.

2-*Anilino*-1 : 2-*benzophenanthridine*.—The foregoing chloro-base (0·1 g.) and aniline (0·2 g.) were heated on a steam-bath for 1 hr. A little 50% alcohol was then added, whereupon the product crystallised. Recrystallisation from aqueous alcohol (charcoal) gave the 2-*anilino*-derivative in almost quantitative yield as pale yellow needles, m. p. 152° (Found : C, 86·1; H, 4·7; N, 8·9. $C_{23}H_{16}N_2$ requires C, 86·2; H, 5·0; N, 8·7%).

1 : 2-*Benzophenanthridine*.—(i) 9-Chloro-1 : 2-benzophenanthridine (1 g.) and potassium hydroxide (0·5 g.) in alcohol (35 c.c.) were hydrogenated over Raney nickel (1 g.; *Org. Synth.*, 1941, **21**, 15) at room temperature and pressure. After 4 hr., 2 mols. of hydrogen had been absorbed and hydrogenation ceased. The filtrate was concentrated to about 10 c.c., and on the addition of a little water the product separated. After recrystallisation from alcohol, 1 : 2-benzophenanthridine (86%) formed colourless prisms, m. p. 136°, alone or mixed with a specimen prepared by zinc dust distillation of 1 : 2-benzophenanthridone (Graebe, *loc. cit.*, gives m. p. 135·5°).

(ii) 1 : 2-Benzophenanthridone (0·5 g.) and lithium aluminium hydride (0·4 g.) in dry dioxan (15 c.c.) were refluxed for 10 hr., cooled, treated with a little water, and filtered. The inorganic residue was washed with hot dioxan, and the filtrate and washings were concentrated. Water was then added and the resulting bright yellow precipitate (presumably the dihydride) collected. After one recrystallisation from alcohol it had m. p. 213°, but further attempted purification in this manner reduced the m. p. considerably. It was dehydrogenated by heating it with 10% platinised asbestos (0·1 g.) in *p*-cymene for 2 hr. Recrystallisation of the product from alcohol gave 1 : 2-benzophenanthridine (95%), m. p. 136°, identical with the product obtained by the previous method.

(iii) 1 : 2-Benzophenanthridine was obtained almost quantitatively by reduction of the 9-chloro-derivative (0·5 g.) with lithium aluminium hydride (0·3 g.) in dry dioxan (15 c.c.) for 8 hr., and dehydrogenation as above.

7 : 8-*Benzophenanthridone*.—(i) Powdered sodium azide (1 g.) was added gradually to a well-stirred solution of 2-*o*-carboxyphenyl-1-naphthoamide (3 g.) in concentrated sulphuric acid (15 c.c.) at 55—60°, as above. After one recrystallisation from chlorobenzene, 7 : 8-benzophenanthridone formed colourless prisms, m. p. 332° (95%). Graebe, *loc. cit.*, gives m. p. 338°.

(ii) 7 : 8-Benzophenanthridone was obtained by oxidation of 2-*o*-benzamido-1-naphthoic acid with sodium hypochlorite according to Graebe (*loc. cit.*). After sublimation under reduced pressure it had m. p. 338°.

9-*Chloro*-7 : 8-*benzophenanthridine*.—7 : 8-Benzophenanthridone (1 g.) was refluxed with phosphorus oxychloride and a little dimethylaniline as described above. The excess of oxychloride was removed *in vacuo*. To facilitate removal of the last traces a little benzene was added and then removed *in vacuo*. The residue was extracted with light petroleum, the solvent evaporated, and the product (0·83 g.) crystallised from benzene and from pure dioxan. 9-*Chloro*-7 : 8-*benzophenanthridine* formed colourless plates, m. p. 163°, from benzene (Found : C, 77·3; H, 3·9; N, 5·0; Cl, 13·6. $C_{17}H_{10}NCl$ requires C, 77·4; H, 3·8; N, 5·3; Cl, 13·45%).

In a preliminary experiment in which no special care was taken to remove traces of phosphorus oxychloride, the residue was extracted with alcohol. The resulting crystalline compound, which contained no chlorine, formed colourless needles, m. p. 125·5°, from alcohol, and was identified as the 9-*ethoxy*-compound (Found : C, 83·8; H, 5·65; N, 5·25. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5; N, 5·1%). The m. p. was not depressed by admixture with a specimen prepared by refluxing the 9-chloro-compound with sodium ethoxide in alcohol.

Hydrolysis of the 9-chloro-compound to 7 : 8-benzophenanthridone was effected in quantit-

ative yield by 1 hour's refluxing in 95% alcohol or in alcoholic hydrochloric acid. It was, however, recovered unchanged following 2 hours' refluxing with ammoniacal alcohol.

The 9-chloro-compound and aniline on the steam-bath (1 hr.) gave the 9-*anilino*-derivative (67%), in pale yellow needles, m. p. 155° (from alcohol) (Found: C, 85·9; H, 4·9; N, 8·9%).

7 : 8-*Benzophenanthridine*.—(i) The 9-chloro-compound was hydrogenated as above (3 hr.), giving 7 : 8-benzophenanthridine as colourless plates (78%), m. p. 183° (from alcohol). The m. p. was not depressed by admixture with a specimen prepared from 7 : 8-benzophenanthridone by zinc dust distillation (Graebe, *loc. cit.*, gave m. p. 182°).

(ii) 7 : 8-Benzophenanthridone and lithium aluminium hydride in dioxan, as above, gave a crude, yellow, unstable dihydride (?), m. p. 261°, dehydrogenated with 10% platinised asbestos in boiling *p*-cymene, to 7 : 8-benzophenanthridine, m. p. 183° (from alcohol), identical with the material obtained as above.

(iii) 7 : 8-Benzophenanthridine was obtained almost quantitatively on reduction of the 9-chloro-compound with lithium aluminium hydride and dehydrogenation of the product with platinised asbestos.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, February 15th*, 1954.]

---

*Steroids. Part XIV.** 7 : 8-*Epoxides of* 9α- *and* 9β-*Ergostan*-11-*one Derivatives.*

By JAMES GRIGOR, WILLIAM LAIRD, DUNCAN MACLEAN, G. T. NEWBOLD, AND F. S. SPRING.

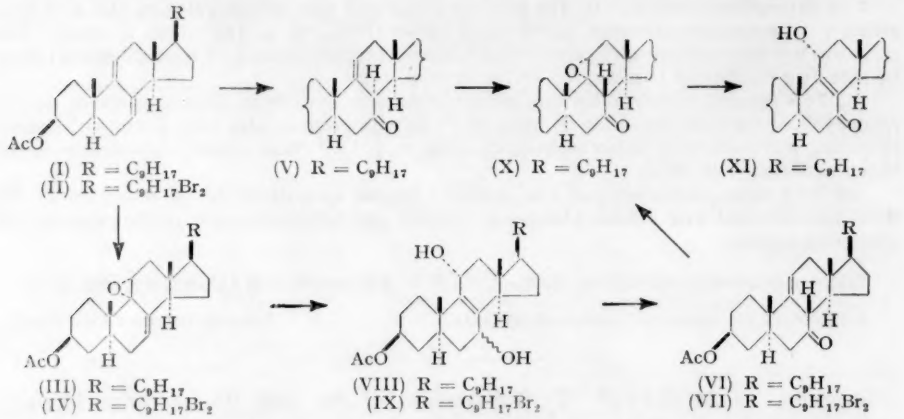
[Reprint Order No. 5118.]

22 : 23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate is isomerised by brief contact with alumina to the 9α-isomer. Oxidation of the latter with perbenzoic acid gives 22 : 23-dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate while similar treatment of the 9β-isomer gives 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate. Both oxo-epoxides are isomerised by hydrogen bromide to 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate. The action of alkali and acid upon the two oxo-epoxides has been studied and the products have been isolated and characterised.

A NUMBER of oxidation products derived from steroid 7 : 9(11)-dienes have been described during the last three years. In particular it is known that oxidation of ergosteryl-D acetate (I) with aromatic peracids gives the 9α : 11α-epoxide (III) (Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; 1953, **75**, 3477; Heusser, Eichenberger, Kurath, Dallenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106) whereas with performic acid the βγ-unsaturated ketone 7-oxo-8α-ergosta-9(11) : 22-dien-3β-yl acetate (V) is produced (Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892; Budziarek, Stevenson, and Spring, *J.*, 1952, 4874; Maclean and Spring, *J.*, 1954, 328). The normal $C_{(8)}$-epimer of (V), 7-oxoergosta-9(11) : 22-dien-3β-yl acetate (VI), is obtained, first, by controlled mineral-acid treatment of 9α : 11α epoxyergosta-7 : 22-dien-3β-ol (Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696) followed by acetylation; secondly, from 7ξ : 11α-dihydroxyergosta-8 : 22-dien-3β-yl acetate (VIII), itself obtained from (III) by treatment with mineral acid (Chamberlin *et al.*, *loc. cit.*; Heusser *et al.*, *loc. cit.*) and by reaction with hydrogen peroxide in acetic acid (Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936); and, thirdly, from 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (IX), obtained from the 7 : 9(11)-diene (II) *via* the oxide (IV), which with the boron trifluoride–ether complex gives the βγ-unsaturated dibromo-ketone (VII), debromination of which gives (VI) (Maclean and Spring, *loc. cit.*). Each of the $C_{(8)}$-epimeric βγ-unsaturated ketones (V) and (VI) has been converted into

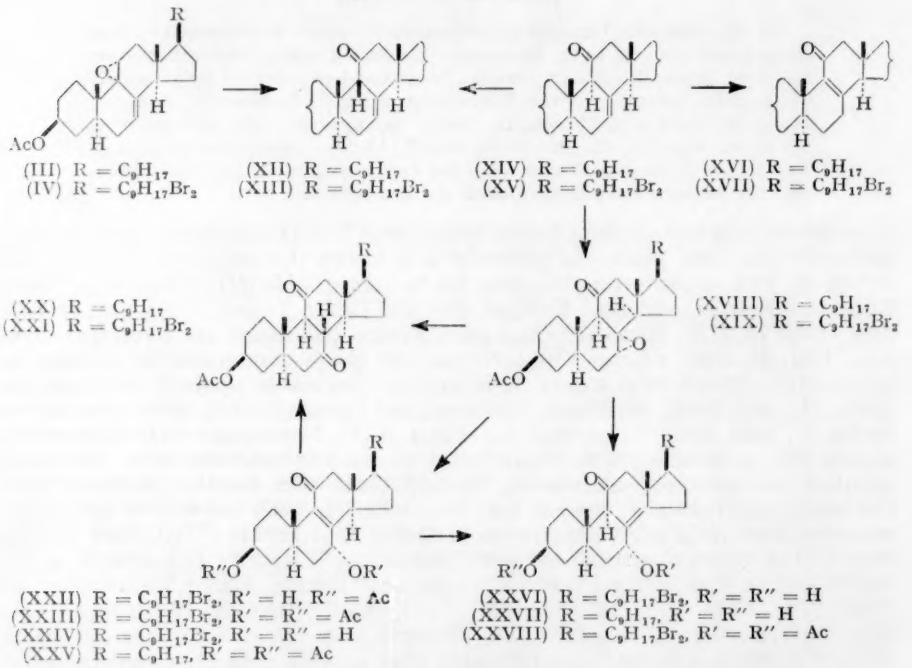
* Part XIII, *J.*, 1954, 1302.

9α : 11α-epoxy-7-oxoergost-22-en-3β-yl acetate (X) (inversion at $C_{(8)}$ occurring in the former case) which although stable to mineral acid is readily converted into 3β : 11α-dihydroxyergosta-8 : 22-dien-7-one (XI) by treatment with alkali (Budziarek, Newbold


(I) R = C_9H_{17}
(II) R = $C_9H_{17}Br_2$
(V) R = C_9H_{17}
(X) R = C_9H_{17}
(XI) R = C_9H_{17}
(III) R = C_9H_{17}
(IV) R = $C_9H_{17}Br_2$
(VIII) R = C_9H_{17}
(IX) R = $C_9H_{17}Br_2$
(VI) R = C_9H_{17}
(VII) R = $C_9H_{17}Br_2$

et al., loc. cit.). The present paper describes the nature and behaviour of the oxidation products derived from two related βγ-unsaturated ketones obtained from steroid 7 : 9(11)-dienes.

In Part X (Maclean and Spring, *loc. cit.*) it was shown that treatment of 22 : 23-dibromo-


(III) R = C_9H_{17}
(IV) R = $C_9H_{17}Br_2$
(XII) R = C_9H_{17}
(XIII) R = $C_9H_{17}Br_2$
(XIV) R = C_9H_{17}
(XV) R = $C_9H_{17}Br_2$
(XVI) R = C_9H_{17}
(XVII) R = $C_9H_{17}Br_2$
(XX) R = C_9H_{17}
(XXI) R = $C_9H_{17}Br_2$
(XVIII) R = C_9H_{17}
(XIX) R = $C_9H_{17}Br_2$
(XXII) R = $C_9H_{17}Br_2$, R′ = H, R″ = Ac
(XXIII) R = $C_9H_{17}Br_2$, R′ = R″ = Ac
(XXIV) R = $C_9H_{17}Br_2$, R′ = R″ = H
(XXV) R = C_9H_{17}, R′ = R″ = Ac
(XXVI) R = $C_9H_{17}Br_2$, R′ = R″ = H
(XXVII) R = C_9H_{17}, R′ = R″ = H
(XXVIII) R = $C_9H_{17}Br_2$, R′ = R″ = Ac

7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (IX) with boron trifluoride gives a mixture from which 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XIII) was isolated, debromination of which yields the corresponding 11-oxo-9β-ergosta-7 : 22-dien-3β-yl

acetate (XII). The βγ-unsaturated ketone (XII) has been obtained by controlled treatment of 9α : 11α-epoxyergosta-7 : 22-dien-3β-yl acetate (III) with the boron trifluoride–ether complex (Heusler and Wettstein, *Helv. Chim. Acta*, **1953**, **36**, 398; Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921), and the βγ-unsaturated ketone (XIII) has been obtained by a similar isomerisation of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (IV) (Elks, Evans, Robinson, Thomas, and Wyman, *J.*, 1953, 2933). During an attempt to obtain an enol acetate of 22 : 23-dibromo-11-oxoergost-8-en-3β-yl acetate by treating the dibromo-epoxide (IV) with boron trifluoride in the presence of acetic anhydride, we found that the reaction gave instead the βγ-unsaturated ketone (XIII). Filtration of a benzene solution of 11-oxo-9β-ergosta-7 : 22-dien-3β-yl acetate (XII) through alumina causes inversion at $C_{(9)}$, to give 11-oxoergosta-7 : 22-dien-3β-yl acetate (XIV) (Bladon *et al.*, *loc. cit.*). Similar treatment of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XIII) gives 22 : 23-dibromo-11-oxoergost-7-en-3β-yl acetate (XV) in good yield. The structure of (XV) was established by its conversion into 11-oxoergosta-7 : 22-dien-3β-yl acetate (XIV) by treatment with zinc dust. If the alumina treatment of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XIII) is prolonged it is isomerised to 22 : 23-dibromo-11-oxoergost-8-en-3β-yl acetate (XVII) (Maclean and Spring, *loc. cit.*), showing that (XV) is an intermediate in the alumina rearrangement of (XIII) into (XVII). In the same way, prolonged contact with alumina converts 11-oxoergosta-7 : 22-dien-3β-yl acetate (XIV) into 11-oxoergosta-8 : 22-dien-3β-yl acetate (XVI) albeit in poor yield. The molecular rotation change associated with the conversion of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate into the 9α-epimer ($\Delta = +930°$) is similar to that associated with the conversion of 11-oxo-9β-ergost-7 : 22-dien-3β-yl acetate into the 9α-epimer ($\Delta = +1070°$).

Treatment of 22 : 23-dibromo-11-oxoergost-7-en-3β-yl acetate (XV) with perbenzoic acid gives, in high yield, 22 : 23-dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (XIX). The structure ascribed to this oxo-epoxide follows from its method of preparation and from reactions which are described below. The oxidation of the isolated 7 : 8-double bond in a normal 5α-steroid to an epoxide has not been previously observed. According to Fieser and Fieser (" Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 1944, p. 245; Fieser and Ourisson, J. *Amer. Chem. Soc.*, 1953, **75**, 4404) oxidation of a Δ^7-5α-stenol with perbenzoic acid proceeds by initial hydroxylation at $C_{(14)}$ and not by 7 : 8-oxide formation. Two steroid 7 : 8-epoxides have been described in the literature; one of these, 7β : 8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (unnatural configuration at $C_{(9)}$) is obtained by oxidation of 11-oxo-9β-ergosta-7 : 22-dien-3β-yl acetate with monoperphthalic acid and is discussed in some detail later in this paper. The second, methyl 3α-acetoxy-7ξ : 8ξ-epoxychol-9(11)-enate, is obtained by oxidation of methyl 3α-acetoxychola-7 : 9(11)-dienate with monoperphthalic acid (Heusser, Anliker, Eichenberger and Jeger, *loc. cit.*).

22 : 23-Dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (XIX) does not show intense selective absorption in the ultra-violet above 2000 Å and the absence of a hydroxyl group was confirmed by its infra-red absorption spectrum. When treated with zinc dust in a neutral solvent, (XIX) is smoothly debrominated to 7α : 8α-epoxy-11-oxoergost-22-en-3β-yl acetate (XVIII).

22 : 23-Dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (XIX) is readily rearranged by mineral acids; with hydrogen bromide in chloroform–acetic acid it gives 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (XXI), the structure of which follows from its ready conversion into the known 7 : 11-dioxoergost-22-en-3β-yl acetate (XX) by treatment with zinc in a neutral solvent. The natural configuration at $C_{(8)}$ and $C_{(9)}$ in (XXI) follows both from this reaction and from its recovery unchanged after alkaline hydrolysis followed by re-acetylation. Treatment of the oxo-epoxide (XIX) with sulphuric acid in dioxan gives 22 : 23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXII) which shows the characteristic ultra-violet absorption spectrum of an αβ-unsaturated ketone. The presence of a hydroxyl group in (XXII) was established by acetylation which yielded a diacetate (XXIII). 22 : 23-Dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXII) is an intermediate in the conversion of the oxo-epoxide (XIX) into the saturated diketone (XXI)

since it is converted into the last compound by treatment with hydrogen bromide in chloroform–acetic acid.

The behaviour of the oxo-epoxide with alkali was next examined. In 1% methanolic potassium hydroxide at *room temperature*, the oxo-epoxide (XIX) gives 22 : 23-dibromo-3β : 7α-dihydroxyergost-8-en-11-one (XXIV), acetylation of which yields the diacetate (XXIII) mentioned above. Treatment of the diol (XXIV) with zinc dust followed by acetylation of the product gives 3β : 7α-diacetoxyergosta-8 : 22-dien-11-one (XXV), also obtained by debromination of (XXIII) with zinc. The diacetate (XXV) has been obtained by Henbest and Wagland (*J.*, 1954, 728) * by the action of acetic acid on 9α : 11α-epoxyergosta-7 : 22-dien-3β-yl acetate (III), followed by oxidation of the intermediate 3β : 7α-diacetoxyergosta-8 : 22-dien-11α-ol with chromic acid.

When treated with *refluxing* methanolic potassium hydroxide the oxo-epoxide (XIX) gives 22 : 23-dibromo-3β : 7α-dihydroxyergost-8(14)-en-11-one (XXVI) which shows the light absorption characteristic of the isolated 8 : 14-double bond (Bladon, Henbest, and Wood, *J.*, 1952, 2737) and is readily acetylated to the diacetate (XXVIII). Debromination of the diol (XXVI) yields 3β : 7α-dihydroxyergosta-8(14) : 22-dien-11-one (XXVII). 22 : 23-Dibromo-3β : 7α-diacetoxyergost-8-en-11-one (XXIV), obtained from the oxo-epoxide (XIX) by treatment with cold alkali, is an intermediate in the conversion of (XIX) into 22 : 23-dibromo-3β : 7α-dihydroxyergost-8(14)-en-11-one (XXVI) since it is converted into the last compound by refluxing methanolic potassium hydroxide.

The 7α : 8α-configuration is ascribed to the epoxide ring in (XIX) in analogy with the established attack from the rear (α) face of Δ^7-stenols by osmium tetroxide–acid. Oxidation of cholest-7-enyl acetate with osmium tetroxide followed by hydrolysis yields cholestane-3β : 7α : 8α-triol (Fieser and Ourisson, *loc. cit.*; Fieser, *Experientia*, 1950, **6**, 312; Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1507); it follows that the hydroxyl groups in each of the unsaturated alcohols (XXII) and XXVI) derived from it are 7α-orientated.

The oxidation of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XIII) with perbenzoic acid was next examined; by using a freshly prepared reagent and mineral acid-free chloroform an almost quantitative yield of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (XXX) was obtained. The oxo-epoxide is also obtained from (XIII) by oxidation with monoperphthalic acid in ether. Debromination of (XXX) by zinc in a neutral solvent gives 7β : 8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (XXIX), previously obtained by Heussler and Wettstein (*loc. cit.*) and Henbest and Wagland (*loc. cit.*) by direct oxidation of (XII) with monoperphthalic acid.

Treatment of the oxo-epoxide (XXX) in chloroform with a trace of hydrobromic acid gives 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII) which shows the characteristic ultra-violet absorption spectrum of an αβ-unsaturated ketone; its infrared spectrum shows peaks characteristic of an αβ-unsaturated ketone, hydroxyl, and acetoxy-groups. The presence of a hydroxyl group was confirmed by acetylation of (XXXIII) to the diacetate (XXXIV). Apart from the orientation of the 7-hydroxyl group, the correctness of the formulation (XXXIII) for the acid-rearrangement product from the oxo-epoxide (XXX) was established by oxidation with chromic acid followed by treatment with zinc dust and acetic acid which yielded 7 : 11-dioxoergost-22-en-3β-yl acetate (XX). It follows that the compound obtained by the action of hydrobromic acid on the oxo-epoxide (XXX) can differ from 22 : 23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXII), the preparation of which is described above, only in the orientation of the hydroxyl group. As a corollary, the epoxide ring in (XXX) has the β-configuration.

It is of interest to comment upon the difference in behaviour of the $C_{(9)}$-epimeric βγ-unsaturated 11-ketones (XIII) and (XV) with perbenzoic acid. The 9α-epimer (XV) is attacked on the rear (α) face, thus following the general rule for similar reactions for steroids with natural configuration. The 9β-epimer (XIII) is attacked on the front (β) face; β-attack on this bond has been established for the addition of hydrogen (Bladon *et al.*, *loc. cit.*). The reason for the difference is disclosed by inspection of models, which show that

* We are grateful to Professor E. R. H. Jones, F.R.S., for sending us a copy of this paper before its general publication.

the 7 : 8-double bond in (XIII) is considerably more accessible from the β-face than is the case with the $C_{(9)}$-α-epimer (XV).

When 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (XXX) is treated with dioxan containing dilute sulphuric acid 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (XXXV) is formed; this shows the ultra-violet absorption spectrum of a $\Delta^{8(14)}$-stenol. The presence of a hydroxyl group in (XXXV) was confirmed by the infra-red absorption spectrum and by acetylation to the diacetate (XXXVI). With zinc in a neutral solvent 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (XXXV) yields 7β-hydroxy-11-oxo-9β-ergosta-8(14) : 22-dien-3β-yl acetate (XXXVII). The 9β-configuration is assigned to (XXXV), (XXXVI), and (XXXVII) because alkaline hydrolysis of the first compound at room temperature gives a diol, the ultra-violet absorption spectrum of which established the presence therein of the 8(14)-double bond. Acetylation of the diol gives a diacetate which differs from (XXXVI) and is consequently considered to be 22 : 23-dibromo-3β : 7β-diacetoxyergost-8(14)-en-11-one (XXXIX), differing from (XXXVI) solely in configuration at $C_{(9)}$. Debromination of the 9α-diacetate (XXXIX) by zinc in a neutral solvent gives 3β : 7β-diacetoxyergosta-8(14) : 22-dien-11-one (XL) which is also obtained from 22 : 23-dibromo-3β : 7β-dihydroxyergost-8(14)-en-11-one (XXXVIII) by debromination to (XLI) followed by acetylation.* Thus the formation of the oxo-epoxide from (XIII) is not accompanied by inversion at $C_{(9)}$. For different reasons the same conclusion was reached by Henbest and Wagland (*loc. cit.*) concerning the structure of the related bromine-free oxo-epoxide (XXIX).

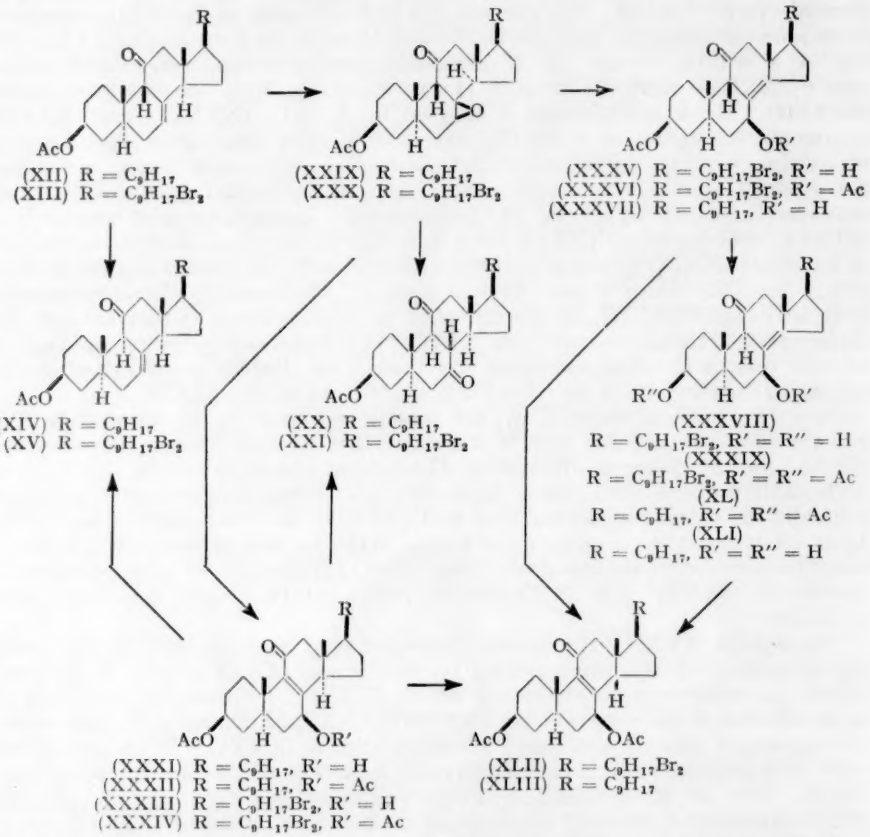
In spite of many attempts, it was not possible to convert the 9β-oxo-epoxide (XXX) into the 9α-isomer. In our view, it is unlikely that the conversion of the oxo-epoxide (XXX) into 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII) proceeds *via* the 9α-oxo-epoxide; when the reaction was followed polarimetrically and spectroscopically the values support the view that (XXXIII) is formed directly from (XXX). Again, oxidation of the βγ-unsaturated ketone (XIII) by perbenzoic acid which had been stored for several days and contained a trace of free hydrogen chloride gave a mixture of the oxo-epoxide (XXX) and 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII).

The acetate (XXXIII) is recovered unchanged after treatment with sulphuric acid in dioxan under conditions which convert the oxo-epoxide (XXX) into 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (XXXV); it follows that (XXXIII) is not an intermediate in the conversion of (XXX) into (XXXV) by mineral acid; this conclusion is in agreement with the established 9β-configuration in (XXXV). When treated with a trace of hydrobromic acid in chloroform under conditions which convert the oxo-epoxide (XXX) into 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII), 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (XXXV) is not converted into (XXXIII) but is dehydrated to give an oxo-diene the structure of which will be discussed in a later paper. In our view this behaviour proves that 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (XXXV) is not an intermediate in the conversion of the oxo-epoxide (XXX) into 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII). When treated with hydrobromic acid in acetic acid–chloroform 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII) is converted into 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (XXI). The diketone (XXI) is also obtained by treatment of the oxo-epoxide (XXX) with hydrobromic acid in acetic acid–chloroform.

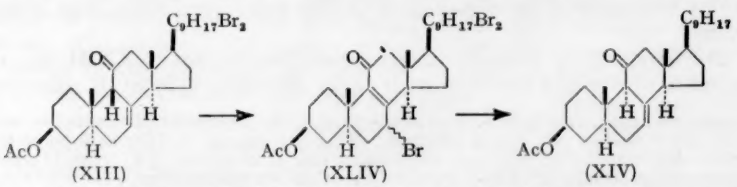
22 : 23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII) was debrominated by means of zinc in a neutral solvent to the related 7β-hydroxy-11-oxoergosta-8 : 22-

* A compound designated 7ξ-hydroxy-11-oxoergosta-8(14) : 22-dien-3β-yl acetate has been obtained by Heusler and Wettstein (*loc. cit.*) by treatment of the oxo-epoxide (XXIX) with boron trifluoride in hot dioxan. Although the m. p. of this compound is similar to that of 7β-hydroxy-11-oxo-9β-ergosta-8(14) : 22-dien-3β-yl acetate (XXXVII), the rotations of the two preparations (+76°, +216° respectively) are markedly different. We have not prepared 7β-hydroxy-11-oxoergosta-8(14) : 22-dien-3β-yl acetate; the related diacetate (XL), m. p. 111—113°, $[\alpha]_D$ +34°, again differs appreciably from the diacetate (m. p. 153—155°) obtained by Heusler and Wettstein. These authors appreciated that their preparation was not pure. Repetition of their experiment did not give a homogeneous product.

dien-3β-yl acetate (XXXI), which gave the 3β : 7β-diacetate (XXXII) (*cf.* Henbest and Wagland, *loc. cit.*). An attempt to debrominate the diacetate (XXXIV) by zinc in a neutral solvent, however, gave 11-oxoergosta-7 : 22-dien-3β-yl acetate (XIV), identical with the product obtained by Bladon *et al.* (*loc. cit.*) by rearrangement of the 9β-isomer


(XII) R = C_9H_{17}
(XIII) R = $C_9H_{17}Br_2$
(XXIX) R = C_9H_{17}
(XXX) R = $C_9H_{17}Br_2$
(XXXV) R = $C_9H_{17}Br_2$, R′ = H
(XXXVI) R = $C_9H_{17}Br_2$, R′ = Ac
(XXXVII) R = C_9H_{17}, R′ = H
(XIV) R = C_9H_{17}
(XV) R = $C_9H_{17}Br_2$
(XX) R = C_9H_{17}
(XXI) R = $C_9H_{17}Br_2$
(XXXVIII)
R = $C_9H_{17}Br_2$, R′ = R″ = H
(XXXIX)
R = $C_9H_{17}Br_2$, R′ = R″ = Ac
(XL)
R = C_9H_{17}, R′ = R″ = Ac
(XLI)
R = C_9H_{17}, R′ = R″ = H
(XXXI) R = C_9H_{17}, R′ = H
(XXXII) R = C_9H_{17}, R′ = Ac
(XXXIII) R = $C_9H_{17}Br_2$, R′ = H
(XXXIV) R = $C_9H_{17}Br_2$, R′ = Ac
(XLII) R = $C_9H_{17}Br_2$
(XLIII) R = C_9H_{17}

(XII) on alumina. Bladon *et al.* found that hydrogenation of (XIV) in an acidic medium gave ergost-8(14)-en-3β-yl acetate (α-ergostenyl acetate), presumably by conjugation of the double bond, hydrogenolysis of the 11-oxygen function, and migration of the double bond. We have confirmed this behaviour and we also find that hydrogenation of (XIV) in ethyl acetate gives 11-oxoergost-7-en-3β-yl acetate previously obtained in a crude form by Bladon *et al.*, using dioxan as solvent. The 9α-ketone (XIV) was also obtained by a related series



of reactions starting from 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XIII). Treatment of (XIII) with bromine gives 7ξ : 22 : 23-tribromo-11-oxoergost-8-en-3β-yl acetate (XLIV) which shows the characteristic ultra-violet absorption spectrum of an

αβ-unsaturated ketone. Treatment of the tribromo-ketone with zinc in a neutral solvent gives 11-oxoergosta-7 : 22-dien-3β-yl acetate (XIV). Thus the behaviour of the epimeric 7-acetoxy-derivatives from 22 : 23-dibromo-11-oxoergost-8-en-3β-yl acetate on treatment with zinc appears to be controlled by the orientation at $C_{(7)}$, the 7α-epimer (XXIII) giving (XXV) by normal side-chain dehalogenation, whereas the 7β-epimer (XXXIV) gives the βγ-unsaturated ketone (XIV). As a consequence we suggest that the bromine attached to $C_{(7)}$ in (XLIV) is β-oriented.

The action of alkali on the oxo-epoxide (XXX) and its two primary acid-rearrangment products (XXXIII) and (XXXV) has been examined. Short treatment of the oxo-epoxide (XXX) with alcoholic alkali and subsequent acetylation yield 22 : 23-dibromo-3β : 7β-diacetoxyergost-8-en-11-one (XXXIV). Prolonged treatment of the oxo-epoxide (XXX) with alkali followed by acetylation gives a mixture from which three homogeneous reaction products have been isolated. One of these is (XXXIV), a second is 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (XXI), and the third is a diacetate $C_{32}H_{48}O_5Br_2$, m. p. 187°. Similar protracted treatment of 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (XXXIII) with alkali followed by acetylation gives a mixture of the diketone (XXI) and the diacetate, m. p. 187°. The diacetate, m. p. 187°, shows the light-absorption properties of an αβ-unsaturated ketone both in the ultra-violet and in the infra-red. It is also obtained from 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (XXXV) by refluxing with alkali followed by acetylation. These relationships, we believe, show that the acetate, m. p. 187°, is 22 : 23-dibromo-3β : 7β-diacetoxy-14β-ergost-8-en-11-one (XLII), differing from (XXXIV) solely in configuration at $C_{(14)}$. In contrast to the behaviour of the 14α-isomer (XXXIV), debromination of (XLII) with zinc in a neutral solvent proceeds normally to give 3β : 7β-diacetoxy-14β-ergosta-8 : 22-dien-11-one (XLIII). It is pertinent to note a remarkable difference in behaviour of 7α- and 7β-hydroxy-substituted 22 : 23-dibromo-11-oxoergost-8-en-3β-yl acetates in refluxing alkali. The 7α-hydroxy-derivative (XXIV) is converted into the non-conjugated 22 : 23-dibromo-3β : 7α-dihydroxyergost-8(14)-en-11-one (XXVI), the double bond moving out of conjugation to give an alkali-stable βγ-unsaturated ketone. In the case of the 7β-hydroxy-derivative (XXXIII), however, similar alkali treatment (followed by acetylation) leads to the 14β-epimer (XLII). This behaviour of the 7β-hydroxy-Δ^8-11-ketone (XXXIII) is the same as that of a related Δ^8-11-ketone of the sapogenin series which epimerises at $C_{(14)}$ on treatment with alkali (Djerassi, Frick, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 3496).

Experimental

Specific rotations were determined in chloroform solution (unless otherwise stated) in a 1-dm. tube at approx. 15°. Ultra-violet absorption spectra were measured in ethanol solution with a Unicam SP.500 spectrophotometer. Infra-red absorption measurements were determined in Nujol suspension.

22 : 23-*Dibromo*-11-*oxo*-9β-*ergost*-7-*en*-3β-*yl Acetate*.—A suspension of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (500 mg.) (Budziarek, Johnson, and Spring, *J.*, 1952, 3410) in dry ether (20 c.c.) and acetic anhydride (15 c.c.) was shaken at room temperature with the boron trifluoride–ether complex (10 drops). Dissolution was complete in 10 min., whereafter solid began to separate. After 1 hr. the solid (220 mg.), m. p. 198°, was collected and crystallised from acetone from which 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate separated as prismatic needles or prisms, m. p. 200° undepressed when mixed with a specimen prepared as described by Maclean and Spring (*loc. cit.*), $[\alpha]_D$ −122° (*c*, 1·1) (Found : C, 58·3; H, 7·5. Calc. for $C_{30}H_{46}O_3Br_2$: C, 58·6; H, 7·55%).

22 : 23-*Dibromo*-11-*oxoergost*-7-*en*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (700 mg.) in light petroleum (b. p. 60—80°)–benzene (1 : 1; 70 c.c.) was adsorbed rapidly under pressure on an alumina column * (10 × 1·5 cm.). The column was immediately eluted with benzene (100 c.c.) containing pyridine (1 c.c.) again under pressure; these operations took 5 min. Evaporation of the filtrate under reduced pressure and crystallis-

* The alumina was prepared as follows: Spence "Type H" alumina (1 kg.) was stirred for 3 hr. with 10% acetic acid (1·5 l.), filtered off, washed with distilled water (2 l.), methanol (2 l.), and distilled water (2 l.) and then reactivated at 400° for 5 hr.

ation of the residue from chloroform–methanol gave 22 : 23-*dibromo*-11-*oxoergost*-7-*en*-3β-*yl acetate* * (620 mg.) as felted needles, m. p. 189—190°, $[\alpha]_D$ +29° (*c*, 0·4) (Found: C, 58·7; H, 7·55. $C_{30}H_{46}O_3Br_2$ requires C, 58·6; H, 7·55%). Light absorption: $\varepsilon_{2060} = 1550$.

11-*Oxoergosta*-7 : 22-*dien*-3β-*yl Acetate*.—22 : 23-Dibromo-11-oxoergost-7-en-3β-yl acetate (306 mg.) in benzene–methanol (1 : 1; 200 c.c.) was refluxed with zinc dust (2 g.) for 2½ hr. Isolation in the usual way followed by crystallisation from methanol gave 11-oxoergosta-7 : 22-dien-3β-yl acetate (150 mg.) as plates, m. p. 176—177°, $[\alpha]_D$ +32° (*c*, 1·0) (Found: C, 79·4; H, 10·6. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%). Light absorption: $\varepsilon_{2040} = 2000$. Bladon *et al.* (*loc. cit.*) give m. p. 175—180°, $[\alpha]_D$ +25°, for a specimen obtained by filtration of a solution of the 9β-epimer through alumina.

11-*Oxoergosta*-8 : 22-*dien*-3β-*yl Acetate*.—A solution of 11-oxoergosta-7 : 22-dien-3β-yl acetate (150 mg.) in benzene–chloroform (10 c.c.; 99 : 1) was adsorbed on a column of Grade II alumina (10 × 2 cm.) and left for 5 days. Elution with benzene (50 c.c.) and crystallisation from methanol gave 11-oxoergosta-8 : 22-dien-3β-yl acetate (30 mg.) as blades, m. p. and mixed m. p. 125—127°, $[\alpha]_D$ +102° (*c*, 0·5). Light absorption: Max. at 2530 Å (ε 8000).

22 : 23-*Dibromo*-7α : 8α-*epoxy*-11-*oxoergostan*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-11-oxoergost-7-en-3β-yl acetate (380 mg.) in chloroform (10 c.c.) at 0° was treated with a freshly prepared solution of perbenzoic acid in mineral acid-free chloroform (2·5 mol.; 2·5 c.c.). The solution was kept at 0° for 8 days, then diluted with chloroform (100 c.c.) and washed successively with saturated sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). The chloroform solution was concentrated under reduced pressure below 35° and diluted with methanol to give 22 : 23-*dibromo*-7α : 8α-*epoxy*-11-*oxoergostan*-3β-*yl acetate* (300 mg.) separating from chloroform–methanol as needles, m. p. 210—212°, $[\alpha]_D$ −17·5° (*c*, 1·7) (Found: C, 57·3; H, 7·6. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·4%). The oxo-epoxide does not show high intensity light absorption above 2000 Å, and it does not give a colour with tetranitromethane in chloroform; it was recovered unchanged after treatment at room temperature with acetic anhydride and pyridine. Infra-red spectrum: peaks at 1747 and 1250 (acetate) and 1717 cm.$^{-1}$ (ketone); no hydroxyl peak.

7α : 8α-*Epoxy*-11-*oxoergost*-22-*en*-3β-*yl Acetate*.—22 : 23-Dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (320 mg.) in benzene–methanol was debrominated in the usual way with zinc. 7α : 8α-*Epoxy*-11-*oxoergost*-22-*en*-3β-*yl acetate* (190 mg.) separates from chloroform–methanol as elongated plates, m. p. 190—191°, $[\alpha]_D$ −15·5° (*c*, 1·3) (Found: C, 76·4; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: $\varepsilon_{2040} = 2100$. It gives a pale yellow colour with tetranitromethane in chloroform.

22 : 23-*Dibromo*-3β : 7α-*dihydroxyergost*-8-*en*-11-*one*.—22 : 23-Dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (275 mg.) in benzene (6 c.c.) was treated with methanolic potassium hydroxide (50 c.c.; 1%) and the solution kept for 3½ hr. at room temperature. Isolation of the product in ether, followed by crystallisation from chloroform–methanol, gave the 3β : 7α-*diol* (240 mg.) as felted needles, m. p. 211°, $[\alpha]_D$ +113°, +112° (*c*, 0·6, 0·7) (Found: C, 56·0; H, 7·5. $C_{28}H_{44}O_3Br_2,CH_3{\cdot}OH$ requires C, 56·1; H, 7·8%). Light absorption: Max. at 2500 Å (ε 9600). Acetylation with acetic anhydride and pyridine at room temperature gives the *diacetate* which separates from methanol as prismatic plates, m. p. 212—213°, $[\alpha]_D$ +104° (*c*, 1·5) (Found: C, 57·2; H, 7·3. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%). Light absorption: Max. at 2460 Å (ε 9400).

3β : 7α-*Diacetoxyergosta*-8 : 22-*dien*-11-*one*.—(*a*) Debromination of 22 : 23-dibromo-3β : 7α-diacetoxyergost-8-en-11-one (500 mg.) by zinc in ether–methanol gives 3β : 7α-diacetoxyergosta-8 : 22-dien-11-one (200 mg.), separating from methanol as fine needles, m. p. 102—103°, $[\alpha]_D$ +109° (*c*, 1·0) (Found: C, 74·9; H, 9·6. Calc. for $C_{32}H_{48}O_5$: C, 75·0; H, 9·4%). Light absorption: Max. at 2490 Å (ε 8800); $\varepsilon_{2040} = 3800$. Henbest and Wagland (*loc. cit.*) give m. p. 102—105°, $[\alpha]_D$ +109°.

(*b*) Treatment of 22 : 23-dibromo-3β : 7α-dihydroxyergost-8-en-11-one (150 mg.) in benzene–methanol with zinc, followed by acetylation of the product with acetic anhydride in pyridine at

* Dr. R. M. Evans (personal communication, March 30th, 1954) writes: "Professor Spring has kindly drawn our attention to the difference in physical properties between the 22 : 33-dibromo-11-oxoergost-7-en-3β-yl acetate as prepared at Glasgow and the compound to which we attributed the same structure (Elks, Evans, Robinson, Thomas, and Wyman, *J.*, 1953, 2933). We have now re-examined our compound and find that it forms a 2 : 4-dinitrophenylhydrazone in greater than 70% yield; we wish, therefore, to withdraw the above structure. Since treatment of our compound with perchloric acid in acetic acid produces material with $\lambda_{max.}$ 2525 Å ($E^{1\%}_{1\,cm.}$ 121) it seems probable that it has a keto-group at $C_{(7)}$, but its physical properties do not agree with those reported for 22 : 23-dibromo-7-oxoergost-9-en-3β-yl acetate (Elks, Evans, Long, and Thomas, *J.*, 1954, 451; Maclean and Spring, *J.*, 1954, 328). Shortage of material has precluded a more thorough examination."

room temperature, gave 3β : 7α-diacetoxyergosta-8 : 22-dien-11-one (50 mg.), separating from methanol as needles, m. p. and mixed m. p. 102—103°, $[\alpha]_D$ +113° (*c*, 0·5).

22 : 23-*Dibromo*-3β : 7α-*dihydroxyergost*-8(14)-*en*-11-*one*.—(*a*) A solution of 22 : 23-dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (320 mg.) in benzene (10 c.c.) and methanolic potassium hydroxide (60 c.c.; 2%) was refluxed for 1½ hr. Concentration under reduced pressure, isolation of the product with ether, and crystallisation from chloroform–methanol gave 22 : 23-*dibromo*-3β : 7α-*dihydroxyergost*-8(14)-*en*-11-*one* (200 mg.) as needles, m. p. 202—203°, $[\alpha]_D$ +33° (*c*, 0·3 in pyridine) (Found: C, 57·2; H, 7·7. $C_{28}H_{44}O_3Br_2$ requires C, 57·15; H, 7·5%). Light absorption: $\varepsilon_{2060} = 8700$. Overnight acetylation of the diol with acetic anhydride in pyridine at room temperature gave the *diacetate* which separates from methanol as needles, m. p. 194—195°, $[\alpha]_D$ +32° (*c*, 1·4) (Found: C, 57·4; H, 7·3. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%). Light absorption: $\varepsilon_{2070} = 8600$.

(*b*) Hydrolysis of 22 : 23-dibromo-3β : 7α-diacetoxyergost-8-en-11-one (140 mg.) with aqueous methanolic potassium hydroxide as in (*a*) gave the 3β : 7α-diol (90 mg.), m. p. and mixed m. p. 202—203°, $[\alpha]_D$ +31° (*c*, 0·2 in pyridine). Light absorption: $\varepsilon_{2060} = 10{,}200$.

3β : 7α-*Dihydroxyergosta*-8(14) : 22-*dien*-11-*one*.—A solution of 22 : 23-dibromo-3β : 7α-dihydroxyergost-8(14)-en-11-one (110 mg.) in benzene–methanol (1 : 1; 50 c.c.) was refluxed with zinc (2 g.) for 2½ hr. Crystallisation of the product from aqueous methanol gave 3β : 7α-*dihydroxyergosta*-8(14) : 22-*dien*-11-*one* (66 mg.) as needles, m. p. 179—181°, $[\alpha]_D$ +8° (*c*, 0·7) (Found: C, 78·4; H, 10·4. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Light absorption: $\varepsilon_{2080} = 7000$.

22 : 23-*Dibromo*-7α-*hydroxy*-11-*oxoergost*-8-*en*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (400 mg.) in benzene (10 c.c.) was refluxed with 2N-sulphuric acid (5 c.c.) in methanol (50 c.c.) for 1 hr. Isolation in ether, followed by crystallisation from chloroform–methanol, gave 22 : 23-*dibromo*-7α-*hydroxy*-11-*oxoergost*-8-*en*-3β-*yl acetate* (130 mg.) as needles, m. p. 216—217°, $[\alpha]_D$ +97° (*c*, 1·8) (Found: C, 56·9; H, 7·1. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35%). Light absorption: Max. at 2490 Å ($\varepsilon = 9000$). Acetylation (acetic anhydride and pyridine on the steam-bath) gave the diacetate which separates from methanol as prismatic plates, m. p. and mixed m. p. 212—213°, $[\alpha]_D$ +100° (*c*, 0·8).

22 : 23-*Dibromo*-7β : 8β-*epoxy*-11-*oxo*-9β-*ergostan*-3β-*yl Acetate*.—(*a*) A solution of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (5·9 g.) in chloroform (70 c.c.) was treated during 1 hr. at 0° with a freshly prepared solution of perbenzoic acid in chloroform (23 c.c.; 62·5 mg./c.c.). After overnight storage at 0° isolation was carried out in the usual way; crystallisation from chloroform–methanol gave 22 : 23-*dibromo*-7β : 8β-*epoxy*-11-*oxo*-9β-*ergostan*-3β-*yl acetate* (5·0 g.) as needles, m. p. 218—221°, $[\alpha]_D$ −29° (*c*, 0·7) (Found: C, 52·7, 52·8; H, 6·9, 7·1; Cl + Br, 30·75. $C_{30}H_{46}O_4Br_2,\frac{1}{2}CHCl_3$ requires C, 53·1; H, 6·8; Cl, 7·7; Br, 23·15%). The solvent of crystallisation was not expelled at 100° *in vacuo*; heating at 135° *in vacuo* was accompanied by decomposition as shown by a change toward dextrorotation and the appearance of high-intensity ultra-violet absorption at 2540 Å. Infra-red spectrum: Peaks at 1730 and 1241 (acetate), 1717 (ketone) and 750 cm.$^{-1}$ (asymmetrical stretching frequency of C–Cl bond). The compound gave no colour with tetranitromethane in chloroform.

(*b*) A suspension of 22 : 23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (1·7 g.) in dry ether (200 c.c.) was refluxed with freshly prepared monoperphthalic acid in ether (8·4 c.c.; 91 mg./c.c.) for 5½ hr. The suspended solid (1·2 g.), m. p. 198—199·5°, $[\alpha]_D$ −122° (*c*, 0·5), was unchanged starting material. The ethereal mother-liquor on storage deposited needles (240 mg.), m. p. 206—215°, $[\alpha]_D$ −36° (*c*, 0·5), which on crystallisation from benzene–light petroleum (b. p. 60—80°) gave 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (200 mg.) as rosettes of fine needles, m. p. 225—226°, $[\alpha]_D$ −29° (*c*, 0·7) (Found: C, 57·4; H, 7·5. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35%). Infra-red spectrum: Peaks at 1731 and 1245 (acetate) and 1715 cm.$^{-1}$ (ketone). It was undepressed in m. p. when mixed with the solvated specimen described above and on crystallisation from chloroform–methanol it gave needles, m. p. 226—227°, containing chloroform of crystallisation.

7β : 8β-*Epoxy*-11-*oxo*-9β-*ergost*-22-*en*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (1·5 g.) in benzene (50 c.c.), moist ether (50 c.c.), and methanol (50 c.c.) was heated under reflux for 5 hr. with zinc dust (5 g.) previously activated by treatment with ammonium chloride. The product, isolated by means of ether, was crystallised from methanol, to give 7β : 8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (1·0 g.) as needles, m. p. 185°, $[\alpha]_D$ −64°, −67° (*c*, 0·5, 1·2) (Found: C, 76·3; H, 10·0. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%). It gives a pale yellow colour in chloroform with tetranitromethane and does not exhibit high-intensity ultra-violet light absorption. Heusler and Wettstein (*loc. cit.*) give

m. p. 170·5—171·5°, $[\alpha]_D$ −74°, for this compound; Henbest and Wagland (*loc. cit.*) record m. p. 175—177°, $[\alpha]_D$ −63°.

7 : 11-*Dioxoergost*-22-*en*-3β-*yl Acetate from* 7β : 8β-*Epoxy*-11-*oxo*-9β-*ergost*-22-*en*-3β-*yl Acetate*.—7β : 8β-Epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (800 mg.) in chloroform (30 c.c.) and acetic acid (60 c.c.) containing aqueous hydrogen bromide (12 drops; 46%) was kept overnight at room temperature. The crude product was crystallised once from methanol, and a solution of the crystalline solid (500 mg.) in benzene–light petroleum (b. p. 60—80°) (100 c.c.; 2 : 1) was filtered through grade II—III alumina (15 × 2 cm.); the column was washed with benzene (200 c.c.). Thereafter benzene (100 c.c.) and benzene–ether (200 c.c.; 19 : 1) eluted a solid (130 mg.), m. p. 198°, crystallisation of which from aqueous methanol gave 7 : 11-dioxoergost-22-en-3β-yl acetate as felted needles, m. p. 198—200° (alone or mixed with a reference specimen), $[\alpha]_D$ −30° (*c*, 1·7) (Found: C, 76·6; H, 9·5. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%).

22 : 23-*Dibromo*-7β-*hydroxy*-11-*oxoergost*-8-*en*-3β-*yl Acetate*.—(*a*) 22 : 23-Dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (500 mg.) in chloroform (10 c.c.) was treated with a solution of aqueous hydrogen bromide (0·05 c.c.; 46%) in chloroform (100 c.c.). The mixture was kept at room temperature for 3 days. The crystalline solid (185 mg.) which had separated was collected and crystallised from chloroform–methanol, to yield 22 : 23-*dibromo*-7β-*hydroxy*-11-*oxoergost*-8-*en*-3β-*yl acetate*, m. p. 232—234°, $[\alpha]_D$ +85° (*c*, 0·4) (Found: C, 57·05; H, 7·55. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35%). Light absorption: Max. at 2540 Å (ε 9000).

(*b*) 22 : 23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (1·2 g.) in chloroform (40 c.c.) was treated with perbenzoic acid in chloroform (4·8 c.c.; 59 mg./c.c.) which had been kept at 0° for 3 weeks before use. The solution was concentrated under reduced pressure to approximately half bulk, then diluted with methanol, and the solid (0·8 g.) was collected and crystallised from chloroform, to give 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (250 mg.) as plates, m. p. 232° alone or mixed with the specimen prepared by method (*a*), $[\alpha]_D$ +78° (*c*, 0·35) (Found: C, 57·15; H, 7·5%). It does not give a colour with tetranitromethane in chloroform. Light absorption: Max. at 2550 Å (ε 10,000). Infra-red spectrum: Peaks at 3461 (hydroxyl), 1737 and 1245 (acetate), and 1661 cm.$^{-1}$ (αβ-unsaturated ketone). From the chloroform mother-liquor 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (200 mg.) was isolated; after crystallisation from chloroform–methanol it separated as needles, m. p. 218—220° undepressed by the specimen previously described, $[\alpha]_D$ −28° (*c*, 0·5) (Found: C, 52·8; H, 6·9%).

7 : 11-*Dioxoergost*-22-*en*-3β-*yl Acetate from* 22 : 23-*Dibromo*-7β-*hydroxy*-11-*oxoergost*-8-*en*-3β-*yl Acetate*.—22 : 23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (85 mg.) suspended in glacial acetic acid (10 c.c.) was treated, with stirring at room temperature, with a solution of chromium trioxide in acetic acid (0·45 c.c.; N) diluted with acetic acid (5 c.c.), added in five equal portions during 1 hr. After a further hour the mixture was heated at 50—60° for 1 hr. and stored overnight at room temperature. The reaction solution was worked up by using ether, and the product dissolved in glacial acetic acid (10 c.c.) and stirred with zinc dust on the steam-bath for 4 hr. Isolation in ether followed by percolation through a short column of Grade II alumina and crystallisation from aqueous methanol gave 7 : 11-dioxoergost-22-en-3β-yl acetate as felted needles, m. p. and mixed m. p. 195—197°, $[\alpha]_D$ −31° (*c*, 0·5) (Found: C, 76·6; H, 10·0. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%).

7β-*Hydroxy*-11-*oxoergosta*-8 : 22-*dien*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (250 mg.) in a mixture of benzene (15 c.c.), methanol (15 c.c.), and ether (15 c.c.) was heated under reflux with activated zinc (1·25 g.) for 5 hr. The product was crystallised from chloroform–methanol from which 7β-*hydroxy*-11-*oxoergosta*-8 : 22-*dien*-3β-*yl acetate* (150 mg.) separated as plates, m. p. 245—246°, $[\alpha]_D$ +104° (*c*, 1·7) (Found: C, 76·5; H, 9·9. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. at 2540 Å (ε = 10,500). 11-Oxoergosta-8 : 22-diene-3β : 7β-diol diacetate was prepared by treatment of the monoacetate with acetic anhydride and pyridine at room temperature; it separates from aqueous methanol as needles, m. p. 152—153°, $[\alpha]_D$ +82° (*c*, 0·7) (Found: C, 74·8; H, 9·4. Calc. for $C_{32}H_{48}O_5$: C, 75·0; H, 9·4%). Light absorption: Max. at 2490 Å (ε 8800). Henbest and Wagland (*loc. cit.*) record m. p. 149—152°, $[\alpha]_D$ +83°.

22 : 23-*Dibromo*-3β : 7β-*diacetoxyergost*-8-*en*-11-*one*.—(*a*) 22 : 23-Dibromo-7β-hydroxy-11-oxo-ergost-8-en-3β-yl acetate (90 mg.) in pyridine (3 c.c.) and acetic anhydride (3 c.c.) was heated on the steam-bath for 1½ hr. Crystallisation of the product from methanol gave the *diacetate* as felted needles, m. p. 169—170°, $[\alpha]_D$ +70° (*c*, 1·2) (Found: C, 57·3; H, 7·3. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%), which did not give a colour with tetranitromethane. Light absorption: Max. at 2500 Å (ε 9200).

(*b*) A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (200 mg.) in

benzene (10 c.c.) and methanolic potassium hydroxide (20 c.c.; 5%) was heated under reflux for 10 min. The precipitated solid was separated, washed with methanol, dried, and heated on the steam-bath for 1 hr. with pyridine (10 c.c.) and acetic anhydride (5 c.c.). Isolation in ether gave 22 : 23-dibromo-3β : 7β-diacetoxyergost-8-en-11-one (100 mg.) which separates from aqueous methanol as felted needles, m. p. and mixed m. p. 170—171°, $[\alpha]_D$ +69° (*c*, 0·6) (Found : C, 56·7; H, 7·15%).

7ξ : 22 : 23-*Tribromo*-11-*oxoergost*-8-*en*-3β-*yl Acetate*.—22 : 23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (1·0 g.) in dry ether (200 c.c.) was treated with a solution of bromine in glacial acetic acid (7·8 c.c.; 0·0316 g./c.c.), added dropwise with stirring at 15°. After being kept for 10 min., the colourless solution was washed with 1% sodium hydroxide solution, then with water, and dried (Na_2SO_4). Crystallisation of the product from chloroform–methanol gave 7ξ : 22 : 23-*tribromo*-11-*oxoergost*-8-*en*-3β-*yl acetate* (800 mg.) as plates, m. p. 198—199° (decomp.), $[\alpha]_D$ +78° (*c*, 1·0) (Found : C, 51·8; H, 6·7. $C_{30}H_{45}O_3Br_3$ requires C, 52·0; H, 6·5%). Light absorption : Max. at 2620 Å (ε 9500).

11-*Oxoergosta*-7 : 22-*dien*-3β-*yl Acetate from* 7ξ : 22 : 23-*Tribromo*-11-*oxoergost*-8-*en*-3β-*yl Acetate*.—A solution of the tribromo-compound (490 mg.) in methanol–ether (70 c.c.; 1 : 1) was refluxed with activated zinc (2 g.), added in portions during 3 hr. Isolation by means of ether gave 11-oxoergosta-7 : 22-dien-3β-yl acetate (280 mg.) which separated from methanol as plates, m. p. and mixed m. p. 175—177°, $[\alpha]_D$ +30° (*c*, 1·1) (Found : C, 79·15; H, 10·4. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%). It gives a pale yellow colour with tetranitromethane in chloroform. Light absorption : $\varepsilon_{2040} = 3400$.

11-*Oxoergosta*-7 : 22-*dien*-3β-*yl Acetate from* 22 : 23-*Dibromo*-3β : 7β-*diacetoxyergost*-8-*en*-11-*one*.—Treatment of the diacetate named (226 mg.) in refluxing benzene–methanol–ether (1 : 1 : 1; 75 c.c.) with activated zinc (2 g.) for 5½ hr. gave 11-oxoergosta-7 : 22-dien-3β-yl acetate (120 mg.) separating from methanol as plates, m. p. 174—176°, $[\alpha]_D$ +29° (*c*, 1·1) (Found : C, 79·1; H, 10·1%). Hydrogenation of this βγ-unsaturated ketone over platinum in acetic acid gave ergost-8(14)-en-3β-yl acetate (α-ergostenyl acetate) as plates from methanol, m. p. 107—109°, $[\alpha]_D$ +3° (*c*, 1·4) (Found : C, 81·6; H, 11·4. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%). The m. p. of a mixture with an authentic specimen, m. p. 109—110°, $[\alpha]_D$ +4° (*c*, 2·0), was undepressed.

11-*Oxoergost*-7-*en*-3β-*yl Acetate*.—A solution of 11-oxoergosta-7 : 22-dien-3β-yl acetate (250 mg.) in ethyl acetate (200 c.c.) was shaken in hydrogen for 24 hr. with platinum (from 60 mg. of PtO_2). Crystallisation of the product from methanol gave 11-*oxoergost*-7-*en*-3β-*yl acetate* (160 mg.) as needles, m. p. 162—164°, $[\alpha]_D$ +48°, +47° (*c*, 1·1, 1·5) (Found : C, 79·15; H, 10·8. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). For a crude (not analysed) specimen of this compound, Bladon *et al.* (*loc. cit.*) give m. p. 145—156°, $[\alpha]_D$ +32°. Light absorption : $\varepsilon_{2050} = 3500$.

22 : 23-*Dibromo*-7β-*hydroxy*-11-*oxo*-9β-*ergost*-8(14)-*en*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (1·19 g.) in dioxan (230 c.c.) was treated with sulphuric acid (8 c.c.; 2N) and stored at room temperature for 4 hr. The solution was diluted with water, and the product isolated by means of ether and crystallised from methanol. The first crop (40 mg.), which showed high-intensity absorption at 2540 Å, was rejected. Concentration of the mother-liquor and crystallisation of the solid obtained from aqueous methanol gave 22 : 23-*dibromo*-7β-*hydroxy*-11-*oxo*-9β-*ergost*-8(14)-*en*-3β-*yl acetate* (940 mg.) as plates, m. p. 201—202°, $[\alpha]_D$ +196° (*c*, 1·5) (Found : C, 57·0; H, 7·6. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35%). It gives a yellow colour with tetranitromethane in chloroform. Light absorption : $\varepsilon_{2110} = 9000$. Infra-red spectrum : Peaks at 3470 (hydroxyl), 1740 and 1250 (acetate) and 1710 cm.$^{-1}$ (ketone). Acetylation with acetic anhydride–pyridine at room temperature gave 22 : 23-*dibromo*-3β : 7β-*diacetoxy*-9β-*ergost*-8(14)-*en*-11-*one* which separated from methanol as plates, m. p. 170—171°, $[\alpha]_D$ +142° (*c*, 1·0) (Found : C, 57·1; H, 7·5. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%). Light absorption : $\varepsilon_{2100} = 8400$.

7β-*Hydroxy*-11-*oxo*-9β-*ergosta*-8(14) : 22-*dien*-3β-*yl Acetate*.—22 : 23-Dibromo-7β-hydroxy-11-oxoergost-8(14)-en-3β-yl acetate (250 mg.) was debrominated with activated zinc dust in benzene–ether–methanol, and the product crystallised from aqueous acetone to give 7β-*hydroxy*-11-*oxo*-9β-*ergosta*-8(14) : 22-*dien*-3β-*yl acetate* (130 mg.) as plates, m. p. 192—195°, $[\alpha]_D$ +216° (*c*, 1·45) (Found : C, 75·35; H, 9·9. $C_{30}H_{46}O_4.C_3H_6O$ requires C, 75·0; H, 9·9%). It gives a yellow colour in chloroform with tetranitromethane. Light absorption : $\varepsilon_{2090} = 8000$.

Dehydration of 22 : 23-*Dibromo*-7β-*hydroxy*-11-*oxo*-9β-*ergost*-8(14)-*en*-3β-*yl Acetate*.—A solution of the acetate (420 mg.) in chloroform (10 c.c.) was treated with aqueous hydrogen bromide (0·05 c.c.; 46%) in chloroform (10 c.c.) and kept at 15° for 4 days. The mixture was diluted with chloroform, and the product isolated in the usual manner. Crystallisation from chloroform–methanol gave the *dienone* (80 mg.) as plates, m. p. 215—217°, $[\alpha]_D$ +24° (*c*, 1·25) (Found :

C, 58·8; H, 7·6. $C_{30}H_{44}O_3Br_2$ requires C, 58·8; H, 7·2%). Light absorption: Max. at 2640 Å (ε 9000). It gives a red-brown colour with tetranitromethane in chloroform.

22 : 23-*Dibromo*-3β : 7β-*dihydroxyergost*-8(14)-*en*-11-*one*.—A solution of 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (1·8 g.) in methanol (150 c.c.) was treated with potassium hydroxide (2·0 g.) in water (5 c.c.) and kept at room temperature for 16 hr. The crystalline solid was separated at −50°, washed with water, and crystallised from chloroform–methanol from which the 3β : 7β-*diol* (1·25 g.) separated as elongated plates, m. p. 207—209°, $[\alpha]_D$ +85° (*c*, 0·5) (Found: C, 55·6; H, 7·9. $C_{28}H_{44}O_3Br_2,2CH_3{\cdot}OH$ requires C, 55·2; H, 8·0%). Light absorption: $\varepsilon_{2090} = 10{,}500$.

Treatment of the diol with acetic anhydride–pyridine on the steam-bath for 3 hr., isolation by means of ether, and crystallisation from methanol gave the *diacetate* as prismatic needles, m. p. 183—185°, $[\alpha]_D$ +55° (*c*, 1·0 on specimen dried at room temperature; drying at 100° causes decomposition accompanied by a change in rotation) (Found: C, 56·8; H, 7·3. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%). Light absorption of air-dried specimen: $\varepsilon_{2080} = 11{,}000$.

3β : 7β-*Dihydroxyergosta*-8(14) : 22-*dien*-11-*one*.—Debromination of the preceding diol (500 mg.) in ether–methanol with zinc gave, after crystallisation of the product from aqueous acetone, 3β : 7β-*dihydroxyergosta*-8(14) : 22-*dien*-11-*one* (320 mg.) as plates, m. p. 166—168°, $[\alpha]_D$ +76° (*c*, 1·4) (Found: C, 78·3; H, 10·1. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Light absorption: $\varepsilon_{2080} = 11{,}500$.

3β : 7β-*Diacetoxyergosta*-8(14) : 22-*dien*-11-*one*.—(*a*) The diol with acetic anhydride and pyridine at room temperature overnight gave the *diacetate*, plates (from aqueous methanol), m. p. 111—113°, $[\alpha]_D$ +34° (*c*, 2·0) (Found: C, 74·6; H, 9·4. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%). Light absorption: $\varepsilon_{2120} = 9000$.

(*b*) Treatment of 22 : 23-dibromo-3β : 7β-diacetoxyergost-8(14)-en-11-one (700 mg.) in ether–methanol with zinc gave 3β : 7β-diacetoxyergosta-8(14) : 22-dien-11-one (480 mg.) which separates from aqueous methanol as plates, m. p. and mixed m. p. 111—113°, $[\alpha]_D$ +35° (*c*, 2·0). Light absorption: $\varepsilon_{2120} = 9200$.

22 : 23-*Dibromo*-7 : 11-*dioxoergostan*-3β-*yl Acetate*.—(*a*) A solution of 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (250 mg.) in chloroform (15 c.c.) containing aqueous hydrogen bromide (8 drops; 46%) was kept overnight. The product was isolated in the usual manner and crystallised from chloroform–methanol, to give 22 : 23-*dibromo*-7 : 11-*dioxoergostan*-3β-*yl acetate* (170 mg.) as fine needles, m. p. 263° (decomp.), $[\alpha]_D$ −5° (*c*, 1·3) (Found: C, 57·4; H, 7·4. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35%). The diketone does not give a colour with tetranitromethane in chloroform and does not show high-intensity ultra-violet absorption.

(*b*) A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (400 mg.) in chloroform (25 c.c.) was treated with glacial acetic acid (50 c.c.) containing aqueous hydrobromic acid (10 drops; 46%) and kept overnight at room temperature. After dilution of the mixture with water the product was isolated by means of chloroform, and the solid crystallised from chloroform–methanol, to give 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (90 mg.) as fine needles, m. p. and mixed m. p. 263° (decomp.), $[\alpha]_D$ −2° (*c*, 1·3) (Found: C, 56·75; H, 7·5%).

(*c*) Similar treatment of 22 : 23-dibromo-7α : 8α-epoxy-11-oxoergostan-3β-yl acetate (300 mg.) under the conditions described in (*b*) gave 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (160 mg.) which separated from methanol as fine needles, m. p. and mixed m. p. 262° (decomp.), $[\alpha]_D$ −3° (*c*, 1·1) (Found: C, 57·2; H, 7·4%).

(*d*) A solution of 22 : 23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (200 mg.) in chloroform (10 c.c.), acetic acid (20 c.c.) and aqueous hydrogen bromide (5 drops; 46%) was kept at room temperature overnight. Isolation in the usual way followed by crystallisation from chloroform–methanol gave 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (80 mg.) as needles, m. p. and mixed m. p. 261—262°, $[\alpha]_D$ −2° (*c*, 1·0) (Found: C, 57·3; H, 7·5%).

7 : 11-*Dioxoergost*-22-*en*-3β-*yl Acetate*.—22 : 23-Dibromo-7 : 11-dioxoergostan-3β-yl acetate (200 mg.) was treated with activated zinc dust in benzene–ether–methanol. The product, isolated by means of ether, separated from methanol giving 7 : 11-dioxoergost-22-en-3β-yl acetate as felted needles, m. p. and mixed m. p. 197—199°, $[\alpha]_D$ −30° (*c*, 0·8) (Found: C, 76·45; H, 9·9. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%).

Treatment of 22 : 23-*Dibromo*-7β : 8β-*epoxy*-11-*oxo*-9β-*ergostan*-3β-*yl Acetate with Alkali*.—A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (1·0 g.) in benzene (25 c.c.) and methanolic potassium hydroxide (55 c.c.; 10%) was refluxed for 4 hr. The solution was concentrated under reduced pressure, diluted with water, and extracted with ether to give an extract and an ether-insoluble solid (147 mg.), m. p. 235°, which were separated.

Acetylation of the solid with acetic anhydride and pyridine gave 22 : 23-dibromo-3β : 7β-diacetoxyergost-8-en-11-one which separated from aqueous methanol as felted needles, m. p. 170—171°, $[\alpha]_D$ +70° (*c*, 0·5) (Found : C, 57·0; H, 7·4%). Infra-red spectrum : Peaks at 1734 and 1235 (acetate) and 1682 cm.$^{-1}$ (αβ-unsaturated ketone).

The ether solution was evaporated and the residue acetylated with acetic anhydride–pyridine on the steam-bath for 1 hr. The solid product, isolated by means of ether, was digested with methanol, and the insoluble fraction (80 mg.; m. p. 240°) collected and crystallised from chloroform–methanol to give 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate as fine needles, m. p. and mixed m. p. 263° (decomp.), $[\alpha]_D$ −3° (*c*, 1·5) (Found : C, 57·4; H, 7·6%).

3β : 7β-*Diacetoxy*-22 : 23-*dibromo*-14β-*ergost*-8-*en*-11-*one*.—(*a*) On standing, the methanol digest described above deposited prismatic needles (350 mg.), m. p. 175°, crystallisation of which from aqueous acetone gave 3β : 7β-*diacetoxy*-22 : 23-*dibromo*-14β-*ergost*-8-*en*-11-*one* (250 mg.) as needles, m. p. 187°, $[\alpha]_D$ +61°, +62° (*c*, 1·0, 0·9) (Found : C, 57·5; H, 7·3. $C_{32}H_{48}O_5Br_2$ requires C, 57·1; H, 7·2%). Light absorption : Max. at 2440 Å (ε = 9200). Infra-red spectrum : Peaks at 1737 and 1241 (acetate) and 1689 cm.$^{-1}$ (αβ-unsaturated ketone).

(*b*) A solution of 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (150 mg.) in methanolic potassium hydroxide (50 c.c.; 2%) was heated under reflux for 2 hr. Isolation by means of ether followed by treatment of the product with acetic anhydride and pyridine at room temperature gave a solid, crystallisation of which from aqueous acetone yielded 3β : 7β-diacetoxy-22 : 23-dibromo-14β-ergost-8-en-11-one (100 mg.) as needles, m. p. 184—186°, $[\alpha]_D$ +63° (*c*, 1·3) (Found : C, 57·4; H, 7·35%). Light absorption : Max. at 2430 Å (ε = 8500).

(*c*) Alkali treatment of 22 : 23-dibromo-3β : 7β-dihydroxyergost-8(14)-en-11-one exactly as in (*b*), followed by acetylation, gave 3β : 7β-diacetoxy-22 : 23-dibromo-14β-ergost-8-en-11-one which separated from aqueous acetone as needles, m. p. and mixed m. p. 185—186°, $[\alpha]_D$ +62° (*c*, 0·9). Light absorption : Max. at 2440 Å (ε = 8900).

3β : 7β-*Diacetoxy*-14β-*ergosta*-8 : 22-*dien*-11-*one*.—Debromination of 3β : 7β-diacetoxy-22 : 23-dibromo-14β-ergost-8-en-11-one (100 mg.) by activated zinc in benzene–ether–methanol gave 3β : 7β-*diacetoxy*-14β-*ergosta*-8 : 22-*dien*-11-*one* (40 mg.), separating from methanol as needles, m. p. 82—84° (softening at 65°), $[\alpha]_D$ +103° (*c*, 0·9) (Found : C, 72·9; H, 9·3. $C_{32}H_{48}O_5$,MeOH requires C, 72·75; H, 9·6%). Light absorption : Max. at 2460 Å (ε = 8400).

Rearrangement of 22 : 23-*Dibromo*-7β-*hydroxy*-11-*oxoergost*-8-*en*-3β-*yl Acetate with Alkali*.—A solution of 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (250 mg.) in benzene (20 c.c.) and methanolic potassium hydroxide (40 c.c.; 5%) was heated under reflux for 4 hr. The product was isolated by using ether and heated with acetic anhydride (4 c.c.) and pyridine (4 c.c.) on the steam-bath for 1 hr. Isolation by using ether gave a gum which crystallised from chloroform–methanol to give 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (40 mg.) as needles, m. p. and mixed m. p. 263° (decomp.), $[\alpha]_D$ −5° (*c*, 1·8) (Found : C, 57·4; H, 7·6%). Concentration of the first chloroform–methanol mother liquor gave a solid which after recrystallisation from aqueous acetone yielded 3β : 7β-diacetoxy-22 : 23-dibromo-14β-ergost-8-en-11-one as needles, m. p. 187—188°, $[\alpha]_D$ +64° (*c*, 1·2) (Found : C, 56·9; H, 7·5%). Light absorption : Max. at 2430 Å (ε = 9000).

We thank Glaxo Laboratories Ltd., Greenford, for financial assistance and for gifts of chemicals, the Department of Scientific and Industrial Research for Maintenance Awards (to D. M. and W. L.), the Governors of The Royal Technical College for the award of the James Young Exhibition (to J. G.), and the Cross Trust for a scholarship (to J. G.). We also thank Dr. A. C. Syme and Mr. Wm. McCorkindale for the microanalyses and ultra-violet absorption measurements, and Mr. A. Pajaczkowski, B.Sc., for the infra-red absorption spectra.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, February 12th*, 1954.]

Introduction of the 11-*Oxo- and the* 11α-*Hydroxy-group into Ring* C *Unsubstituted Steroids. Part IX.* The Epoxides of* $\Delta^{7:9(11)}$-5α-*Hydroxysapogenins.*

By Carl Djerassi, A. J. Lemin, G. Rosenkranz, and Franz Sondheimer.

[Reprint Order No. 5191.]

Diosgenin (I) has been converted by known reactions into 9α : 11α-epoxy-22*a*-spirost-7-en-3β : 5α-diol (V*b*) which on oxidation and subsequent combined dehydration-rearrangement afforded 22*a*-spirosta-4 : 8-dien-3 : 11-dione (VIII). The preparation and some transformation products of 7α : 8α : 9α : 11α-diepoxy-22*a*-spirostan-3β : 5α-diol (IX) are described.

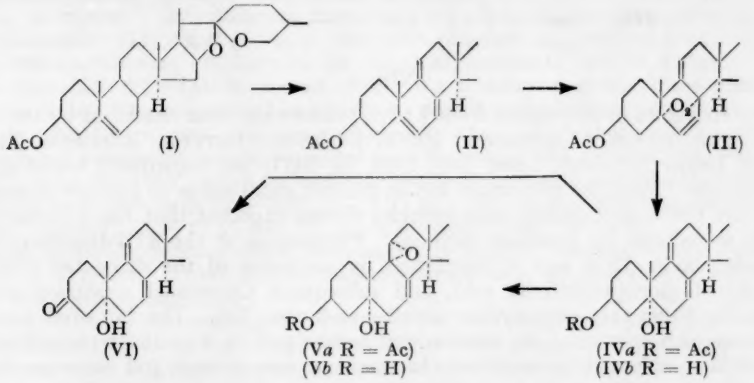
With one exception (Laubach, Schreiber, Agnello, Lightfoot, and Brunings, *J. Amer. Chem. Soc.*, 1953, **75**, 1514) all the chemical methods for the introduction of an 11-oxygen function into steroids unsubstituted in ring C involve oxidation of a 7 : 9(11)-diene (cf. Hems, *J. Pharm. Pharmacol.*, 1953, **5**, 409; Spring, *Progress in Org. Chem.*, 1953, **2**, 104; Djerassi, *Vitamins and Hormones*, 1953, **11**, 205; Rosenkranz and Sondheimer, *Fortschr. Chemie Org. Naturstoffe*, 1953, **10**, 274). Two of these approaches in the ergosterol series proceed through epidioxides (11 : 14, Laubach *et al.*, *loc. cit.*; 5 : 8, Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, Wood, and Woods, *J.*, 1952, 4883). The latter method possesses the advantage of retaining a 5α-hydroxyl group until the last step (Bladon, Henbest, Jones, Lovell, and Woods, *J.*, 1954, 125), thus simplifying considerably the ultimate elaboration of the Δ^4-3-oxo-moiety which otherwise has to be performed in a somewhat round-about fashion (Rosenkranz, Djerassi, Yashin, and Pataki, *Nature*, 1951, **168**, 28).

At an early stage of our work on the partial synthesis of adrenal cortical hormones *via* 11-oxygenated sapogenins, we prepared the 5α : 8α-epidioxide (III) of 3β-acetoxy-22*a*-spirosta-5 : 7 : 9(11)-triene (II), itself readily available from diosgenin (I) (Rosenkranz, Romo, Batres, and Djerassi, *J. Org. Chem.*, 1951, **16**, 298). Subsequent manipulations with this substance, however, yielded erratic results and this approach was abandoned in favour of alternative routes (Djerassi and Rosenkranz, *Ciba Foundation Colloquia on Endocrinology*, 1953, **7**, 79; Rosenkranz, Sondheimer, Mancera, Pataki, Ringold, Romo, Djerassi, and Stork, *Recent Progress in Hormone Research*, 1953, **8**, 1). When we were informed by Prof. E. R. H. Jones (cf. Henbest and Jones, *Ciba Foundation Colloquia on Endocrinology*, 1953, **7**, 39) of the smooth reduction of 3β-acetoxy-5α : 8α-epidioxyergosta-6 : 9 : 22-triene by means of a Raney nickel catalyst to the corresponding 5α-hydroxy-7 : 9(11) : 22-triene (Bladon *et al.*, *loc. cit.*) it appeared of interest to apply these conditions to the corresponding epidioxide (III) in the sapogenin series, and the present paper describes its preparation and some subsequent transformation products.

The epidioxide (III) was prepared essentially according to the method of Windaus and Linsert (*Annalen*, 1928, **465**, 148; cf. Bladon *et al.*, *loc. cit.*). Owing to the high altitude at which the reaction was carried out (7500 feet) no irradiation apart from sunlight was necessary and an alcoholic solution of the triene (II) plus eosin, standing in open vessels, furnished in good yield the desired epidioxide (III). Its structure was adduced from its physical properties (absence of selective absorption in the ulra-violet region), by analogy with the corresponding ergosterol derivative, and by its subsequent reactions. When shaken with Raney nickel in an atmosphere of hydrogen, the epidioxide was smoothly reduced to the 3β-acetoxy-5α-hydroxy-7 : 9(11)-diene (IV*a*); mild hydrolysis then gave the 3 : 5-dihydroxy-diene (IV*b*). The ultra-violet absorption spectra of both compounds (IV*a* and *b*) confirmed their formulation as conjugated dienes. Moreover, since acetylation of the diol (IV*b*) regenerated the original monoacetate (IV*a*), no rearrangement could have taken place during the hydrolysis.

* Part VIII, *J. Amer. Chem. Soc.*, 1953, **75**, 3505.

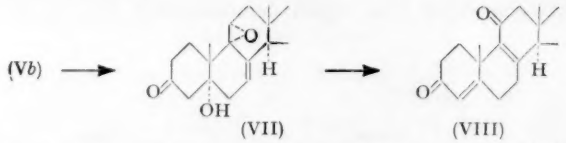
Treatment of the diol (IV*b*) with one mol. of monoperphthalic acid gave (in over 90% yield) the 9α : 11α-monoepoxide (V*b*) which showed no selective ultra-violet absorption. In a similar manner, epoxidation of the 3-acetoxy-5-hydroxy-7 : 9(11)-diene (IV*a*) produced the expected 3-acetoxy-9α : 11α-epoxide (V*a*) which on mild hydrolysis furnished the 3 : 5-dihydroxy-epoxide (V*b*). Completion of the interconversions was accomplished by the acetylation of the 3 : 5-dihydroxy-epoxide (V*b*) back to the corresponding 3-acetoxy-compound (V*a*), again demonstrating that no rearrangement had



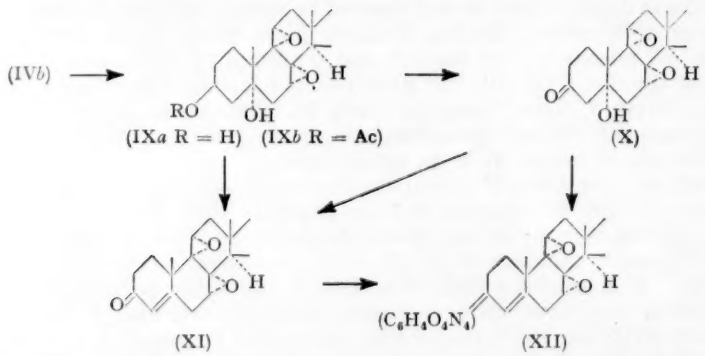
taken place during the hydrolysis of the acetoxy-monoepoxide. The formulation of the monoepoxides as the 9α : 11α-isomers is assumed by analogy with the previous work on the oxidations of $\Delta^{9(11)}$-steroids (Bladon, Henbest, Jones, Wood, Eaton, and Wagland, *J.*, 1953, 2916 and references cited therein), and confirmed by their subsequent reactions. Oxidation of the diol (IV*b*) with the pyridine–chromic anhydride complex (Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422) resulted in the formation of the 3-oxo-compound (VI) without concomitant dehydration and this experiment was used as a model for subsequent oxidations in the epoxide series.

Introduction of the 3-oxo-Δ^4-system was then attempted since it seemed possible that hydrogenation of such an unsaturated 3-oxo-α-epoxide might produce a dihydro-ketone of the 5β-series thus allowing the easy re-introduction of the Δ^4-double bond at a later stage. However, Oppenauer oxidation of the dihydroxy-monoepoxide (V*b*) afforded only highly coloured oils. As it seemed possible that dehydration of the 5α-hydroxy-3-oxo- to the 3-oxo-Δ^4-system could occur under conditions similar to those used in the conversion of Δ^7-9α : 11α-epoxides into the corresponding unsaturated 11-ketones (*i.e.*, treatment with the boron trifluoride–ether complex; Heusser, Eichenberger, Kurath, Dällenbach and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106), oxidation of the diol monoepoxide (V*b*) to the 5α-hydroxy-3-oxomonoepoxide (VII) was attempted with a view to combining the dehydration and the rearrangement into one operation. The use of boron trifluoride as a dehydrating agent (in acetic acid solution) has been described by Davey, Halsall, Jones, and Meakins (*J.*, 1951, **2696**) who, by treatment of 18β-oleanane-3β : 19β : 28-triol 3 : 28-diacetate obtained an unsaturated diacetate indicating that the loss of the axial hydroxyl group had occurred by *trans*-elimination. The required selective oxidation of the 3β-hydroxyl group of the monoepoxy-diol (V*b*) was carried out with the pyridine–chromic anhydride complex as described for the model compound but optimum yields were obtained only when a large excess of pyridine was used. The product, 9α : 11α-epoxy-3-oxo-22*a*-spirost-7-en-5α-ol (VII), on treatment for 2 minutes with two mols. of boron trifluoride–ether complex in refluxing benzene, gave 22*a*-spirosta-4 : 8-dien-3 : 11-dione (VIII), the structure of which was proved as follows. The infra-red absorption spectrum showed only *one* band in the carbonyl region, the position of which (at 1665 cm.$^{-1}$) indicated the presence of one or more αβ-unsaturated ketonic systems. The high intensity of the peak suggested that more than one such system was present, a conclusion confirmed by the

preparation of the 3-mono-2 : 4-dinitrophenylhydrazone which still showed a peak in the absorption spectrum (at 1665 cm.$^{-1}$) though of reduced intensity. The analyses of the diketone and its 3-hydrazone together with their ultra-violet absorption spectra also supported the formulation (VIII). An investigation of the catalytic and chemical reduction products of this compound is under way.



The preparation of diepoxides from 7 : 9(11)-dienes has been described by two groups (Bladon *et al., loc. cit.*; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1953, **75**, 3477) but subsequent transformations have been few. Since the diepoxides are, in general, more stable to hydrolytic rearrangements than the corresponding monoepoxides it was expected that the 3-oxo-Δ^4-system could be introduced by standard methods. Preparation of the 3 : 5-dihydroxy-7α : 8α-9α : 11α-diepoxide (IX*a*) was accomplished by oxidation of the diene-diol (IV*b*) with two mols. of monoperphthalic acid, and subsequent Oppenauer oxidation gave the required 7α : 8α-9α : 11α-diepoxy-22α-spirost-4-en-3-one (XI). The infra-red and ultra-violet absorption spectra of the unsaturated ketone and its 2 : 4-dinitrophenylhydrazone indicated that only one unsaturated chromophore was present and therefore that the diepoxy-grouping had remained intact.



Oxidation of the diepoxy-diol (IX*a*) with the pyridine–chromic anhydride complex again furnished a 5α-hydroxy-3-oxo-compound (X) which by dehydration with aluminium *iso*propoxide in toluene, or by preparation of the semicarbazone followed by cleavage with pyruvic acid, led to the 7α : 8α-9α : 11α-diepoxy-22a-spirost-4-en-3-one (XI) previously prepared. As was to be expected, both (X) and (XI) reacted with 2 : 4-dinitrophenylhydrazine to give the same hydrazone (XII). The conversion of (XI) into cortisone will be reported elsewhere (Lewis and Djerassi, *J. Amer. Chem. Soc.*, 1954, in the press).

Experimental

M. p.s were determined on a Kofler block, rotations were measured in chloroform solution in a 1-dm. tube at room temperature (20—25°), and ultra-violet light absorption measurements were made in ethanol unless otherwise stated. Infra-red spectra were determined with a Baird Associates model B double-beam recording spectrophotometer with sodium chloride optics.

3β-*Acetoxy*-5α : 8α-*epidioxy*-22a-*spirosta*-6 : 9(11)-*diene* (III).—A solution of 3β-acetoxy-22*a*-spirosta-5 : 7 : 9(11)-triene (II) (20 g.) and eosin (0·044 g.) in dry ethanol (4·4 l.) was allowed to stand in open vessels in direct sunlight for 5 hr., after which the solvent was removed and the

residue crystallised from chloroform–methanol, to give 3β-*acetoxy*-5α : 8α-*epidioxy*-22a-*spirosta*-6 : 9(11)-*diene* (III) (15·1 g.), m. p. 233—235°, $[\alpha]_D$ +15° (Found : C, 71·7; H, 8·4. $C_{29}H_{40}O_6$ requires C, 71·9; H, 8·3%). Only end-absorption was shown in the ultra-violet region.

3β-*Acetoxy*-22a-*spirosta*-7 : 9(11)-*dien*-5α-*ol* (IV*a*).—A solution of the epidioxide acetate (III) (3·0 g.) in dioxan (75 c.c.) was hydrogenated in the presence of Raney nickel (*ca.* 3 c.c. of thick sludge prepared according to Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471, and pre-reduced in dioxan). The uptake of hydrogen was 230 c.c. (corresponding to 2·2 mols. at 570 mm.), after which the catalyst was filtered off, the filtrate diluted with water, and the white precipitate collected, washed, and dried, to yield 2·8 g. of the crude product, $\lambda_{max.}$ 242 mμ (ε 13,800). Crystallisation from chloroform–hexane gave 3β-*acetoxy*-22a-*spirosta*-7 : 9(11)-*dien*-5α-*ol* (IV*a*) (2·41 g.), m. p. 263—265°, $[\alpha]_D$ −6°, $\lambda_{max.}$ 242 mμ (ε 15,200), $\nu_{max.}$ (in $CHCl_3$) 1736 cm.$^{-1}$ (Found : C, 73·7; H, 8·9. $C_{29}H_{42}O_5$ requires C, 74·0; H, 9·0%).

22a-*Spirosta*-7 : 9(11)-*dien*-3β : 5α-*diol* (IV*b*).—To a solution of the diene-acetate (IV*a*) (0·5 g.) in dioxan (30 c.c.) and methanol (200 c.c.) was added a solution of potassium carbonate (0·8 g.) in water (10 c.c.), and the mixture refluxed for 1 hr. Removal of one-half of the solvent under reduced pressure followed by precipitation of the steroid with water led to a crude product (0·47 g.), m. p. 205—210°, which on crystallisation from methanol gave 22a-*spirosta*-7 : 9(11)-*dien*-3β : 5α-*diol* (IV*b*), m. p. 214—216°, $[\alpha]_D$ ±0°, $\lambda_{max.}$ 242 mμ (ε 14,600), $\nu_{max.}$ (in $CHCl_3$) 3470, 3650 cm.$^{-1}$ (Found : C, 75·4; H, 9·5. $C_{27}H_{40}O_4$ requires C, 75·7; H, 9·4%).

Acetic anhydride–pyridine (room temperature, overnight) regenerated the diene-acetate (IV*a*), m. p. 261—263°, $[\alpha]$ −8° (infra-red absorption spectrum identical with that of the diene-acetate previously prepared).

3β-*Acetoxy*-9α : 11α-*epoxy*-22a-*spirost*-7-*en*-5α-*ol* (V*a*).—A solution of 3β-acetoxy-22*a*-spirosta-7 : 9(11)-dien-5α-ol (IV*a*) (4·0 g.) in chloroform (30 c.c.) was treated with monoperphthalic acid (1 equiv.) in ether and kept at room temperature for 2 days. The needles which had been deposited were filtered off, washed with aqueous sodium hydrogen carbonate and then water, and dried, yielding the crude monoepoxide acetate (3·1 g.), m. p. 295—298°. The chloroform–ether filtrate was washed with sodium hydrogen carbonate solution and water and on evaporation gave an additional 0·5 g. of crude monoepoxide acetate, m. p. 283—286°. Crystallisation of either product from methanol afforded the same 3β-*acetoxy*-9α : 11α-*epoxy*-22a-*spirost*-7-*en*-5α-*ol* (V*a*), m. p. 299—301°, $[\alpha]_D$ −42°, $\nu_{max.}$ (in $CHCl_3$) 1730 cm.$^{-1}$ having no selective absorption in the ultra-violet region (Found : C, 71·7; H, 9·0. $C_{29}H_{42}O_6$ requires C, 71·6; H, 8·7%).

9α : 11α-*Epoxy*-22a-*spirost*-7-*en*-3β : 5α-*diol* (V*b*).—(a) *By hydrolysis of* 3β-*acetoxy*-9α : 11α-*epoxy*-22a-*spirost*-7-*en*-5α-*ol* (V*a*). The hydrolysis of the monoepoxy-acetate (V*a*) was carried out as described for the preparation of 22*a*-spirosta-7 : 9(11)-dien-3β : 5α-diol (IV*b*) and afforded 9α : 11α-*epoxy*-22a-*spirost*-7-*en*-3β : 5α-*diol* (V*b*) in 85% yield. The analytical sample after crystallisation from acetone had m. p. 226—228°, $[\alpha]_D$ −60° (no selective ultra-violet absorption), $\nu_{max.}$ (in $CHCl_3$) 3510, 3690 cm.$^{-1}$ (Found : C, 72·8; H, 9·2. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1%).

(b) *By monoperphthalic acid oxidation of* 22a-*spirosta*-7 : 9(11)-*dien*-3β : 5α-*diol* (IV*b*). A solution of the diene-diol (IV*b*) (3·2 g.) in methylene chloride (50 c.c.) was treated with monoperphthalic acid in ether (10 c.c. of a 1·5N-solution) and kept for 12 hr. at room temperature. Dilution with methylene chloride (100 c.c.), and washing with dilute sodium hydrogen carbonate solution and water, followed by evaporation, gave the crude epoxide (3·1 g.), m. p. 221—225°, which on crystallisation from acetone had m. p. 225—227°, and an infra-red absorption curve identical with that of the mono-epoxy-diol (V*b*) prepared by method (a).

Acetylation with acetic anhydride–pyridine (room temp., overnight) gave the monoepoxy-acetate (V*a*), m. p. 298—300°, with an infra-red absorption curve indistinguishable from that of the sample previously prepared.

9α : 11α-*Epoxy*-3-*oxo*-22a-*spirost*-7-*en*-5α-*ol* (VII).—Chromic anhydride (1·5 g.) was dissolved in pyridine (150 c.c.), cooled in ice-water, and added to a solution of the monoepoxy-diol (V*b*) (1·44 g.) in pyridine, and the whole was set aside for 14 hr. at room temperature. Dilution with much water followed by extraction with ether, washing with very dilute hydrochloric acid and water, evaporation, and crystallisation from acetone–hexane furnished 9α : 11α-*epoxy*-3-*oxo*-22a-*spirost*-7-*en*-5α-*ol* (1·2 g.) (VII), m. p. 236—238°, $[\alpha]_D$ −40°, no selective absorption in the ultra-violet, $\nu_{max.}$ (in $CHCl_3$) 3420, 1702 cm.$^{-1}$ (Found : C, 72·8; H, 8·6. $C_{27}H_{38}O_5$ requires C, 73·3; H, 8·65%).

22a-*Spirosta*-4 : 8-*dien*-3 : 11-*dione* (VIII).—A solution of the keto-monoepoxide (VII) (0·5 g.) was dissolved in dry benzene (100 c.c.), and solvent (10 c.c.) was distilled off to ensure anhydrous conditions. Boron trifluoride–ether (0·5 c.c.) was then added and the mixture

refluxed for 2 min., whereafter the reaction was immediately stopped by addition of water. The organic layer was diluted with ether, washed with water, and evaporated, to yield a yellow semisolid material (0·46 g.) which on chromatography on deactivated alumina (neutral, Brockmann III) and elution with benzene–ether (9 : 1) followed by crystallisation from acetone–hexane gave 22a-*spirosta*-4 : 8-*dien*-3 : 11-*dione* (VIII) (0·135 g.), m. p. 205—206°, $[\alpha]_D$ +289°; $\lambda_{max.}$ 236—242 mμ (ε 20,800), $\nu_{max.}$ (in $CHCl_3$) 1665 cm.$^{-1}$ (Found: C, 76·25; H, 8·25. $C_{27}H_{36}O_4$ requires C, 76·4; H, 8·55%). The 2 : 4-*dinitrophenylhydrazone* (prepared according to Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003), after crystallisation from chloroform–methanol, had m. p. 258—260°, $\lambda_{max.}$ (in $CHCl_3$) 389 mμ (ε 29,800) $\nu_{max.}$ (in $CHCl_3$) 1665 cm.$^{-1}$ (Found: N, 9·8. $C_{33}H_{40}O_7N_4$ requires N, 10·0%).

5α-*Hydroxy*-22a-*spirosta*-7 : 9(11)-*dien*-3-*one* (VI).—Chromic anhydride–pyridine oxidation of the dien-diol (IV*b*) (1·0 g.) was carried out as described for the preparation of the keto-monoepoxide (VII) and afforded, after crystallisation from acetone–hexane, 5α-*hydroxy*-22a-*spirosta*-7 : 9(11)-*dien*-3-*one* (VI) (0·91 g.), m. p. 248—250°, $[\alpha]$ +10°, $\lambda_{max.}$ 243 mμ (ε 15,900), $\nu_{max.}$ (in $CHCl_3$) 3450, 3640, 1705 cm.$^{-1}$ (Found: C, 75·8; H, 8·8. $C_{27}H_{38}O_4$ requires C, 76·0; H, 9·0%).

7α : 8α-9α : 11α-*Diepoxy*-22a-*spirostan*-3β : 5α-*diol* (IX*a*).—A solution of the dien-diol (IV*b*) (1·0 g.) in methylene chloride (15 c.c.) was treated with ethereal monoperphthalic acid (10 c.c. of a 1·05N-solution) and kept at room temperature overnight. Working up as described for the preparation of the monoepoxy-diol (V*b*) and crystallisation from acetone gave 7α : 8α-9α : 11α-*diepoxy*-22a-*spirostan*-3β : 5α-*diol* (IX*a*) (0·91 g.), m. p. 277—280°, $[\alpha]_D$ −72°, no selective absorption in the ultra-violet, $\nu_{max.}$ (in $CHCl_3$) 3500, 3680 cm.$^{-1}$ (Found: C, 70·4; H, 8·9. $C_{27}H_{40}O_6$ requires C, 70·4; H, 8·75%).

Acetylation by acetic anhydride–pyridine gave 3β-*acetoxy*-7α : 8α-9α : 11α-*diepoxy*-22a-*spirostan*-5α-*ol* (IX*b*), m. p. 340—344°, $[\alpha]_D$ −59°, no selective absorption in the ultra-violet, $\nu_{max.}$ (in $CHCl_3$) 3450, 1730, 1243 cm.$^{-1}$ (Found: C, 69·2; H, 8·1. $C_{29}H_{42}O_7$ requires C, 69·3; H, 8·4%).

7α : 8α-9α : 11α-*Diepoxy*-5α-*hydroxy*-22a-*spirostan*-3-*one* (X).—The diepoxy-diol (IX*a*) (0·5 g.) in pyridine (15 c.c.) was treated with chromic anhydride (0·5 g.) in pyridine (50 c.c.) as described for the preparation of the keto-monoepoxide (VII). The resulting 7α : 8α-9α : 11α-*diepoxy*-5α-*hydroxy*-22a-*spirostan*-3-*one* (X) (0·44 g.) crystallised from methanol, and had m. p. 282—284°, $[\alpha]_D$ −52°, no selective absorption in the ultra-violet, $\nu_{max.}$ (in $CHCl_3$) 3410, 1705 cm.$^{-1}$ (Found: C, 70·4; H, 8·1. $C_{27}H_{38}O_6$ requires C, 70·7; H, 8·35%).

7α : 8α-9α : 11α-*Diepoxy*-22a-*spirost*-4-*en*-3-*one* (XI).—(a) *By Oppenauer oxidation of the diepoxy-diol* (IX*a*). A solution of the diepoxy-diol (IX*a*) (0·17 g.) in toluene (17 c.c.) and *cyclo*hexanone (0·17 c.c.) was distilled until 4 c.c. of distillate had been collected. Aluminium *iso*propoxide (0·4 g.) in toluene (3 c.c.) was added and the mixture slowly distilled for 30 min., 5 c.c. of distillate being then obtained. The inorganic material was taken into solution with sodium potassium tartrate solution, the whole was diluted with ether, and the ethereal layer washed with water and evaporated under reduced pressure. The last traces of solvent were removed azeotropically with water. The resulting sticky solid (0·17 g.) was crystallised from acetone–hexane, to give 0·08 g. of 7α : 8α-9α : 11α-*diepoxy*-22a-*spirost*-4-*en*-3-*one* (XI), m. p. 262—264°, $[\alpha]_D$ +46°, $\lambda_{max.}$ 239 mμ (ε 14,600), $\nu_{max.}$ (in $CHCl_3$) 1665 cm.$^{-1}$ with no hydroxyl band (Found: C, 73·8; H, 8·2. $C_{27}H_{36}O_5$ requires C, 73·6; H, 8·2%).

(b) *By dehydration of the keto-diepoxide* (X) *with aluminium* iso*propoxide in toluene.* A solution of the keto-diepoxide (X) (0·2 g.) in toluene (20 c.c.) was distilled until 2 c.c. of distillate had been collected. A solution of aluminium *iso*propoxide (0·4 g.) in toluene (5 c.c.) was added and distillation continued for 20 min., whereafter sodium potassium tartrate solution was added and the product worked up as described in the Oppenauer oxidation to give the ketone (XI) (0·19 g.), m. p. 261—263°, identical with the previously prepared sample.

(c) *By cleavage of the semicarbazone of the keto-diepoxide* (X). A solution of the keto-diepoxide (X) (0·1 g.) in pyridine (10 c.c.) and ethanol (10 c.c.) was heated on a steam-bath for 1½ hr. with semicarbazide hydrochloride (0·05 g.). Dilution with water and extraction with ether gave a semisolid semicarbazone which was cleaved directly (18 hr., room temperature) by being dissolved in ethanol (10 c.c.), acetic acid (1 c.c.), 50% pyruvic acid (1 c.c.) (cf. Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 486). Dilution with water, extraction with ether, washing with dilute sodium hydroxide solution (5%) and water, followed by evaporation and crystallisation from acetone–hexane, gave the ketone (XI) (0·08 g.), m. p. 260—263°.

The 2 : 4-*dinitrophenylhydrazone* (XII) prepared from (XI) crystallised from chloroform–methanol and had m. p. 273—275°, $\lambda_{max.}$ (in $CHCl_3$) 387 mμ (ε 28,900) (Found: N, 9·3.

$C_{33}H_{40}O_8N_4$ requires N, 9·0%). The same hydrazone was obtained from 7α : 8α-9α : 11α-diepoxy-5α-hydroxy-22*a*-spirostan-3-one (X) by the standard acetic acid procedure (Djerassi, *loc. cit.*).

One of the authors (A. J. L.) acknowledges the award of the Syntex Post-doctorate Fellowship at Wayne University which enabled him to participate in this investigation. The analyses were done by Mr. J. F. Alicino, Metuchen, N.J., and Geller Laboratories, Hackensack, N.J. We are grateful to Srta. Mercedes Velasco for valuable preparative assistance.

Department of Chemistry, Wayne University, Detroit, Michigan.
Research Laboratories, Syntex, S.A., Mexico City. [*Received, March 9th*, 1954.]

Reducing Action of Glycols in Alkaline Medium. Part I. Mechanism of Formation of Stilbenes from Substituted Benzaldehydes.

By Wadie Tadros, Labib Ekladius, and Alfy Badie Sakla.

[Reprint Order No. 5097.]

Stilbenes, alcohols, and acids are formed when substituted benzaldehydes are heated with sodium dissolved in ethylene glycol. Neither hydrobenzoins nor deoxybenzoins are intermediates in the formation of stilbenes. The alcohols were also obtained by reducing the aldehydes with lithium aluminium hydride.

Anisoin, hydroanisoin, and deoxyanisoin are excluded as intermediates in the formation of 4 : 4′-dimethoxystilbene from *p*-anisaldehyde by alkaline ethylene glycol (Tadros and Ekladius, *Nature*, 1950, **166**, 525). Hydroanisoin was recovered unchanged after several hours' refluxing. Deoxyanisoin gave mainly 1 : 2-di-*p*-methoxyphenylethanol and *p*-hydroxyphenyl 4-methoxybenzyl ketone. The structure of the latter product was proved by comparison of the ethylation products with the two possible isomers synthesised by Friedel–Crafts reactions with stannic chloride (Wilds and Biggerstaff, *J. Amer. Chem. Soc.*, 1845, **67**, 789; see also Carter and Hey, *J.*, 1948, 150), and by degradation of the ethylated ketone by fusion with sodium hydroxide to *p*-ethoxybenzoic acid.

On similar treatment anisoin gave hydroanisoin and a little deoxyanisoin. Anisil was obtained when anisoin was heated in alkaline glycerol (Tadros and Ekladius, *loc. cit.*).

o- and *m*-Alkoxy- and *p*-dimethylamino-benzaldehydes gave also the corresponding stilbenes, alcohols, and acids. The alkoxybenzyl alcohols were also obtained by reduction of the aldehydes with lithium aluminium hydride.

When injected subcutaneously in sesame oil into 5 ovariectomised 22-g. mice, 4 : 4′-bisdimethylaminostilbene (dose, 5 mg. in 0·4 c.c.; 4 × 0·1 c.c. during 2 days) had no œstrogenic activity.

Experimental

Action of Sodium 2-Hydroxyethoxide in Glycol on Substituted Benzaldehydes.—The procedure and products obtained are exemplified by the following. Anisaldehyde (16·8 g., 0·1 mol.) and a solution of sodium (1·4 g., 0·06 g.-atom) or sodium hydroxide (2·4 g., 0·06 mol.) in ethylene glycol (30 c.c.) were refluxed for 3·5—4 hr. The mixture was diluted with water, and the precipitate was filtered off. Recrystallisation from acetic acid or benzene gave colourless 4 : 4′-dimethoxystilbene, m. p. 214° (1·25 g.). The acetic acid or benzene mother-liquors contained an unidentified resin (8 g.). The turbid alkaline filtrate was extracted with ether. Ether was left to evaporate at room temperature and the residue was crystallised from light petroleum (b. p. 50—60°) from which anisyl alcohol, m. p. 25°, separated [*p*-nitrobenzoate, m. p. and mixed m. p. 93—94° (Mozingo and Folkers, *J. Amer. Chem. Soc.*, 1948, **70**, 229)]. Acidification of the alkaline solution with hydrochloric acid gave anisic acid, m. p. and mixed m. p. 184°.

Other *stilbenes* (yield, 6—8%) (see Table 1) crystallised from acetic acid, benzene, or toluene and were colourless except the bisdimethylamino-compound (pale yellow). The alcohols

(yield, 8—10%; also obtained quantitatively by reducing the aldehydes with lithium aluminium hydride, see below) and the acids (yield, 4%) are reported in Table 2.

Products obtained from Deoxyanisoin.—Deoxyanisoin (6 g.) and sodium (0·7 g.) in ethylene glycol (15 c.c.) were refluxed for 3 hr. On dilution with water 1 : 2-di-*p*-methoxyphenyl-

TABLE 1. *Stilbenes*, $C_6H_4R{\cdot}CH{:}CH{\cdot}C_6H_4R$.

R	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
o-MeO [a, b]	136°	79·6	6·5	$C_{16}H_{16}O_2$	80·0	6·7
m-MeO [b, c]	98	79·3	6·3	$C_{16}H_{16}O_2$	80·0	6·7
p-MeO [a–h]	214	80·0	6·5	$C_{16}H_{16}O_2$ *	80·0	6·7
o-EtO [b]	88	80·2	7·7	$C_{18}H_{20}O_2$	80·6	7·5
p-EtO [b, d, h, i]	207	80·0	7·3	$C_{18}H_{20}O_2$	80·6	7·5
p-Pr^{n}O [j]	194—195	81·0	8·1	$C_{20}H_{24}O_2$	81·1	8·1
p-Pr^{i}O	145	80·8	8·0	$C_{20}H_{24}O_2$	81·1	8·1
p-Bu^{n}O	187	81·7	9·1	$C_{22}H_{28}O_2$	81·5	8·6
p-*n*-$C_5H_{11}O$	174	82·1	8·8	$C_{24}H_{32}O_2$	81·8	9·1
p-*n*-$C_7H_{15}O$	158—159	82·3	9·2	$C_{28}H_{40}O_2$	82·4	9·8
p-*n*-$C_8H_{17}O$	155	82·2	10·1	$C_{30}H_{44}O_2$	82·6	10·1
p-Me_2N [k]	260	80·4	8·0	$C_{18}H_{22}N_2$ †	81·2	8·3

* Found: MeO, 25·0. Calc.: MeO, 25·0%. † Found: N, 9·7. Calc.: N, 10·5%.

[a] Kopp, *Ber.*, 1892, **25**, 600. [b] Pascal and Normand, *Bull. Soc. chim.*, 1911, **9**, 1059. [c] Kopp, *Annalen*, 1893, **277**, 339. [d] Wiechell, *ibid.*, 1894, **279**, 337. [e] Brand and Matsui, *Ber.*, 1913, **46**, 2942. [f] Stobbe and Hensel, *Ber.*, 1926, **59**, 2254. [g] Sah and Yuin, *Chem. Abs.*, 1947, **41**, 5869. [h] Brand, *Ber.*, 1913, **46**, 2935. [i] Frankforter and Kritchevsky, *J. Amer. Chem. Soc.*, 1914, **36**, 1511. [j] Also prepared (Tadros and Aziz) by refluxing a benzene (50 c.c.) solution containing 2 : 2 : 2-trichloro-1 : 1 : di-(*p*-*n*-propoxyphenyl)ethane (Stephenson and Waters, *J.*, 1946, 339) (0·6 g.) and powdered sodium (0·1 g.) for 16 hr.; filtration and concentration gave the stilbene, m. p. and mixed m. p. 194—195°. [k] Campaigne and Budde, *Chem. Abs.*, 1950, **44**, 4478, give m. p. 253—254°. The *n*-propoxy- to *n*-octyloxy-stilbenes are new.

TABLE 2.

Substituent	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
		Benzyl alcohols.				
m-MeO [a]	29—30°	69·4	7·5	$C_8H_{10}O_2$	69·6	7·2
3 : 5-dinitrobenzoate [b]	120—121	N, 9·1		$C_{15}H_{12}O_7N_2$	N, 8·4	
o-EtO [c]	31—32	71·0	7·4	$C_9H_{12}O_2$	71·1	7·9
3 : 5-dinitrobenzoate [b]	109	N, 8·1		$C_{16}H_{14}O_7N_2$	N, 8·1	
p-EtO [d]	27	71·2	7·7	$C_9H_{12}O_2$	71·1	7·9
p-Pr^{n}O [e]	28—29	72·7	8·8	$C_{10}H_{14}O_2$	72·3	8·4
p-Pr^{i}O	27—28	71·7	8·5	$C_{10}H_{14}O_2$	72·3	8·4
p-Bu^{n}O	30—31	73·0	8·8	$C_{11}H_{16}O_2$	73·3	8·9
p-n-$C_5H_{11}O$	33	74·0	9·3	$C_{12}H_{18}O_2$	74·2	9·3
p-*n*-$C_7H_{15}O$	48	76·5	10·0	$C_{14}H_{22}O_2$	75·7	10·0
p-*n*-$C_8H_{17}O$	49	76·3	10·0	$C_{15}H_{24}O_2$	76·3	10·2
p-Me_2N methioodide	232	41·6	5·7	$C_{10}H_{16}ONI$ *	41·0	5·5
		Benzoic acids. [f]				
p-EtO	195	65·1	6·4	$C_9H_{10}O_3$	65·1	6·0
p-Pr^{n}O	141—142	66·0	6·5	$C_{10}H_{12}O_3$	66·7	6·7
p-Pr^{i}O	163	66·6	6·0	$C_{10}H_{12}O_3$	66·7	6·7
p-Bu^{n}O	145—146	67·3	7·0	$C_{11}H_{14}O_3$	68·0	7·2
p-*n*-$C_5H_{11}O$	122	68·8	7·4	$C_{12}H_{16}O_3$	69·2	7·7

* Found: N, 4·8. Calc.: N, 4·8%.

[a] Pschorr (*Annalen*, 1912, **391**, 40) gives b. p. 252°. [b] These dinitrobenzoates were obtained by heating the alcohol (0·5 g., 1·25 ml.), 3 : 5-dinitrobenzoyl chloride (0·7 g., 1 mol.), and a few drops of pyridine on the water-bath for 30 min., and crystallisation from light petroleum (b. p. 50—60°). [c] Pschorr and Zeidler (*ibid.*, 1910, **373**, 75) give b. p. 254°. Bötsch (*Monatsh.*, 1880, **1**, 621) gives b. p. 264°. Hart and Hirschfelder (*J. Amer. Chem. Soc.*, 1921, **43**, 1688) give b. p. 264°/760 mm., 149—150°/28 mm. [d] Braun and Michaelis (*Annalen*, 1933, **507**, 1) give b. p. 134—135°/12 mm. [e] Smith and Burnett, jun. (*Chem. Abs.*, 1950, **44**, 6569) give no details. [f] These acids had m. p.s unchanged on admixture with samples prepared by Jones's method (*J.*, 1935, 1874; see also Cohen and Dudley, *J.*, 1910, 1732). *o*-Ethoxybenzoic acid was identified as the amide, m. p. and mixed m. p. 110° (Limpricht, *Annalen*, 1856, **98**, 256). *m*-Methoxy-, m. p. 105—106° (Graebe, *ibid.*, 1905, **340**, 204) and *p*-dimethylamino-benzoic acid (Zaki and Tadros, *J.*, 1941, 562) had m.p.s unchanged on admixture with authentic samples. *p*-Heptyloxy- and *p*-octyloxy-benzoic acid were obtained in very small quantities.

ethanol separated and was filtered off. It had m. p. 110° (0·8 g.) (from dilute acetic acid) (Found : C, 74·2; H, 6·8. Calc. for $C_{16}H_{18}O_3$: C, 74·4; H, 7·0%). Heating the alcohol with concentrated hydrochloric and acetic acid (Buck and Jenkins, *J. Amer. Chem. Soc.*, 1929, **51**, 2163) gave 4 : 4′-dimethoxystilbene, m. p. and mixed m. p. 214°. The alkaline filtrate afforded p-*hydroxyphenyl* 4-*methoxybenzyl ketone* (0·7 g.), m. p. 175° (from dilute alcohol) (Found : C, 74·4; H, 5·8; OMe, 13·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8; OMe, 12·8%).

p-*Ethoxyphenyl* 4-*Methoxybenzyl Ketone*.—(*a*) *p*-Methoxyphenylacetyl chloride (from 1·25 g. of acid; Carter and Hey, *loc. cit.*) in thiophen-free benzene (6 c.c.) and dry phenetole (3·2 c.c.), cooled in ice, was treated with a mixture of anhydrous stannic chloride (2·5 c.c.) and dry benzene (2·5 c.c.), left for 12 hr., then hydrolysed with ice and hydrochloric acid and extracted with ether. The solvent was removed and the residual *ketone* crystallised from alcohol as colourless crystals, m. p. 101—102° (0·8 g.) (Found : C, 75·6; H, 6·6. $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·7%).

4-*Ethoxybenzyl* p-*methoxyphenyl ketone*, similarly prepared, and crystallised from alcohol, had m. p. 100° (0·8 g.) (Found : C, 75·6; H, 6·6%).

(*b*) *p*-Hydroxyphenyl 4-methoxybenzyl ketone (0·5 g.) in alcoholic sodium methoxide (0·05 g. of sodium in 15 c.c. of alcohol) was refluxed for 15 min. Ethyl iodide (1·2 g.) was added and the mixture was refluxed for a further 1·5 hr., then evaporated. The residue, washed with water to remove the sodium iodide and crystallised from alcohol, had m. p. 102° (0·5 g.), alone or mixed with *p*-ethoxyphenyl 4-methoxybenzyl ketone prepared as above, but depressed on admixture with the isomer.

Degradation of the Ketones.—The ketone (0·1 g.) was added to fused sodium hydroxide (0·2 g.) and carefully heated for 0·5 min. The material was dissolved in hot water and filtered, and the filtrate was acidified. The precipitated acids were recrystallised from dilute alcohol. *p*-Ethoxyphenyl 4-methoxybenzyl ketone, obtained by either method, gave *p*-ethoxybenzoic acid, m. p. and mixed m. p. 195°. 4-Ethoxybenzyl *p*′-methoxyphenyl ketone gave *p*-anisic acid, m. p. and mixed m. p. 181°.

Reduction of Anisoin.—Anisoin (10 g.) was refluxed with sodium (2·3 g.) in ethylene glycol (30 c.c.) for ½ hr. Hydroanisoin (2·4 g.), m. p. and mixed m. p. 168°, and deoxyanisoin (0·36 g.), m. p. and mixed m. p. 109—110°, were precipitated on dilution and were separated by fractional crystallisation from alcohol. When heating was for 3½ hr., 4 : 4′-dimethoxystilbene (0·017 g.), m. p. and mixed m. p. 214°, was also obtained.

Oxidation of Anisoin.—Anisoin (10 g.) and sodium (2·4 g.) in glycerol (30 c.c.) were heated at 190—195° for 1½ hr. Dilution and crystallisation from alcohol gave anisil (1 g.), m. p. and mixed m. p. 133° (monoxime, m. p. 131°). On concentration of the alcoholic mother-liquor, unchanged anisoin was recovered.

Reductions by Lithium Aluminium Hydride.—These are exemplified by the following. To an ice–salt-cooled solution of *p*-anisaldehyde (1·36 g., 1 mol.) in dry ether (50 c.c.), powdered lithium aluminium hydride (1·52 g., 4 mol.) was gradually added. The mixture was then refluxed for 1 hr. Excess of lithium aluminium hydride was decomposed by water, added dropwise to the cooled mixture. Dilute acetic acid (1 : 1; 50 c.c.) was added and the ethereal layer was washed with aqueous sodium carbonate and then water. The ethereal solution was dried (Na_2SO_4) and ether was removed. 4-Methoxybenzyl alcohol, crystallised from light petroleum (b. p. 50—60°), had m. p. and mixed m. p. 24—25° (1·35 g.).

2-Methoxybenzyl alcohol was identified as the *p*-nitrobenzoate, m. p. and mixed m. p. 81—82° (Mozingo and Folkers, *loc. cit.*).

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
CAIRO UNIVERSITY, EGYPT.

[*Received, February 8th*, 1954.]

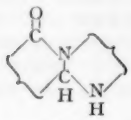
Heterocyclic Nitrogen Compounds. Part IV. Further Condensations with Aldehydic Acids and Diamines.*

By (Miss) E. F. M. Stephenson.

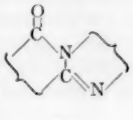
[Reprint Order No. 5147.]

The condensation of phthalaldehydic acids and diamines reported in Part III * has been further investigated. A new preparation of 2′-formyldiphenyl-2-carboxylic acid is given and carbonyl derivatives of this compound are described.

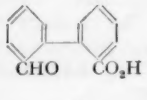
The author (*J.*, 1952, 5024) examined the condensation of *o*-phthalaldehydic acid and 8-formyl-1-naphthoic acid with certain symmetrical diamines and showed the method to be general for the preparation of compounds containing one or other of the systems (A) or (B). This work has now been extended to include an unsymmetrical diamine and also to cover reactions of 2′-formyldiphenyl-2-carboxylic acid (I). A new preparation of (I) (previously prepared by Cook, Dickson, Jack, Louden, McKeown, MacMillan, and Williamson, *J.*, 1950, 139) is described and it has been characterised further by the preparation of several derivatives of its carbonyl group.



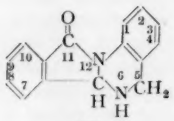
(A)



(B)

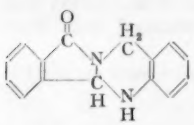


(I)

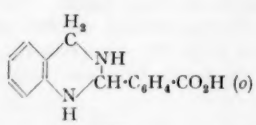


(II)

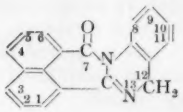
o-Phthalaldehydic acid condenses with *o*-aminobenzylamine to give a compound, m. p. 204·5—205·5°, the presence of the ·CH·NH· system rather than the C:N bond being shown by the formation of *N*-acetyl and *N*-nitroso-derivatives. The product could be (II) or (III), but provisionally has been assigned the former formula on the ground that treatment of the nitroso-derivative with alcoholic hydrogen chloride causes denitrosation (regenerating the parent compound) and not rearrangement of the NO group as would be expected if the N·NO group were attached directly to an aromatic nucleus. Gabriel (*Ber.*, 1912, **45**, 717) by distillation of 2-*o*-carboxyphenyl-1 : 2 : 3 : 4-tetrahydroquinazoline (IV) *in vacuo* obtained a compound, m p. 216—218°, which should have the structure (II) or (III). In our hands Gabriel's method gave erratic results and his product was not obtained pure. However, treatment of (IV) with concentrated sulphuric acid gave the compound, m. p. 204·5°, in small yield.



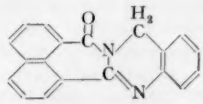
(III)



(IV)



(V)



(VI)

8-Formyl-1-naphthoic acid with *o*-aminobenzylamine gives a small yield of a product with a C:N bond which must have the structure (V) or (VI). To distinguish between these, naphthalic anhydride was condensed with *o*-aminobenzylamine. The main product, *N*-*o*-aminobenzylnaphthalimide, was cyclised in small yield at 300° to (VI), identical with the product from the " aldehydic acid " condensation. Attempts to cyclise the naphthalimide with acetic anhydride gave only a diacetyl derivative [cf. the action of acetic anhydride on *N*-2″-amino-2′-diphenylylnaphthalimide (Stephenson, *loc. cit.*)]. Condensation of 2′-formyldiphenyl-2-carboxylic acid with *o*-phenylenediamine and with 2 : 2′-diaminodiphenyl under varying conditions failed to yield pure products. The former failure may

* Part III, *J.*, 1952, 5024.

be contrasted with the ease of formation of similar products from phthalaldehydic acid and 2 : 2′-diaminodiphenyl (Stephenson, *loc. cit.*) and from diphenic anhydride and *o*-phenylenediamine (Bistrzcyki and Fässler, *Helv. Chim. Acta*, 1923, **6**, 519).

A convenient preparation of 2 : 2′-diaminodiphenyl is described.

Experimental

Microanalyses were made by the C.S.I.R.O. Micro-analytical Service.

o-*Nitrobenzylamine*.—Powdered sodium azide (6·5 g.) was added (7—8 min.) with stirring to a mixture of *o*-nitrophenylacetic acid (7·24 g.), chloroform (40 ml.), and concentrated sulphuric acid (10 ml.), the temperature rising to 30—35°. The mixture was then heated first at 47—48° and then at 43—46° for 3 hr. (stirring), and the chloroform layer decanted and extracted with sodium carbonate solution to remove a little *o*-nitrophenylacetic acid. The sulphuric acid layer was decomposed with crushed ice and, after removal of unchanged *o*-nitrophenylacetic acid (total recovery 3·1—3·3 g.), the *o*-nitrobenzylamine was recovered by making the filtrate strongly alkaline and extracting the product with benzene in a continuous extractor for 9 hr. After removal of the benzene the base was dissolved in ethanol (10 ml.) and addition of concentrated hydrochloric acid (5 ml.) gave *o*-nitrobenzylamine hydrochloride (2·2—2·4 g.), m. p. 248—250° (decomp.). The *benzenesulphonyl* derivative, prepared under Schotten–Baumann conditions, separated from aqueous alcohol (charcoal) in prisms, m. p. 92—93° (Found: C, 53·6; H, 4·1; N, 9·5; S, 11·0. $C_{13}H_{12}O_4N_2S$ requires C, 53·4; H, 4·1; N, 9·6; S, 11·0%). *N*-*o*-Nitrobenzylphthalimide was obtained in ~90% yield by refluxing equimolar amounts of phthalic anhydride and *o*-nitrobenzylamine hydrochloride in glacial acetic acid with excess of anhydrous sodium acetate for 3 hr.; precipitation with water and recrystallisation from acetic acid gave pale cream crystals, m. p. 219—221° [Gabriel (*Ber.*, 1887, **20**, 2227; 1903, **36**, 807) gives m. p. 217·5—219°].

o-*Aminobenzylamine*.—Gabriel and Colman's method (*Ber.*, 1904, **37**, 3644) for the reduction of *o*-nitrobenzylamine proved wasteful. An aqueous solution of *o*-nitrobenzylamine hydrochloride containing 10% excess of sodium acetate was shaken with Raney nickel and hydrogen (at approx. 1 atm.) until the theoretical amount of hydrogen had been absorbed. After removal of the catalyst, the base, m. p. 60—62° (~85%), was obtained by basifying the mixture and continuously extracting it with benzene (9 hr.). It is best converted into its dihydrochloride, m. p. 215—218° (decomp.). Its dibenzoyl derivative (Schotten–Baumann) formed needles [from alcohol (charcoal)], m. p. 195—196° (Found: C, 76·7; H, 5·7. Calc. for $C_{21}H_{18}O_2N_2$: C, 76·3; H, 5·5%).

5 : 6 : 11 : 6a-*Tetrahydro*-11-*oxoisoindolo*[2 : 1-a]*quinazoline* (Ring Index No. 2416) (II).—(i) *o*-Phthalaldehydic acid (0·75 g.), *o*-aminobenzylamine dihydrochloride (0·98 g.), hydrated sodium acetate (1·5 g.), water (22·5 ml.), and acetic acid (12·5 ml.) were refluxed for 8 hr., and, after cooling, the yellow solution was partially neutralised with sodium hydroxide. After 12 hr. the precipitate (1·1 g.) was collected and chromatographed in benzene on alumina (B.D.H.; 2·3 × 10 cm.). The *compound* (II) (0·44 g.) was eluted first as a colourless solution in benzene. Crystallisation from ethanol gave prisms, m. p. 204·5—205·5° (Found: C, 76·4; H, 5·1; N, 12·1. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1; N, 11·9%). The *acetyl* derivative, prepared in boiling acetic anhydride, formed stout prisms, m. p. 163—164·5° (Found: C, 73·5; H, 5·0; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·1; N, 10·1%). The *nitroso*-derivative was obtained when (II) (0·24 g.), in acetic acid (9 ml.) and water (2 ml.) and cooled to 8°, was treated with sodium nitrite (75 mg.) in water (2 ml.). The product (0·26 g.) was precipitated with water and crystallised from ethanol as pale cream, hair-like prisms, m. p. 212·5—213·5° (decomp.) (Found: C, 68·1; H, 4·1; N, 15·8. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·8%). It gave a positive Liebermann's nitroso-reaction, and was decomposed by alcoholic hydrogen chloride with regeneration of (II) (m. p. and mixed m. p.) in nearly quantitative yield.

(ii) 2-*o*-Carboxyphenyl-1 : 2 : 3 : 4-tetrahydroquinazoline (IV) (0·2 g.) and concentrated sulphuric acid (1 ml.) were heated in a boiling-water bath for 7 min., and the clear solution was poured on crushed ice. After basification with ammonia and storage for 12 hr., the product (90 mg.) was collected and chromatographed on alumina (B.D.H.; 1·5 × 5 cm.), being eluted (35 mg.) as a colourless solution by benzene. After crystallisation from ethanol it was identified as (II) by m. p. and mixed m. p.

Condensation of 8-*Formyl*-1-*naphthoic Acid and* o-*Aminobenzylamine*.—8-Formyl-1-naphthoic acid (1 g.), *o*-aminobenzylamine dihydrochloride (1 g.), hydrated sodium acetate (1·5 g.), acetic acid (40 ml.), and water (10 ml.) were refluxed for 7 hr. After partial neutralisation with

sodium hydroxide the mixture was kept for 20 hr. The yellow precipitate (1·6 g.) was collected and chromatographed in benzene on alumina (B.D.H.; 2·5 × 35 cm.), dark by-products being more strongly adsorbed and the product (140 mg.) eluted as a bright yellow solution in benzene. Repeated crystallisation from ethanol gave long, thin, yellow-orange prisms, m. p. 211—212° (Found: C, 80·4; H, 4·2; N, 10·1. $C_{19}H_{12}ON_2$ requires C, 80·3; H, 4·3; N, 9·9%). This compound (VI), 7-*oxo*-7H : 9H-8 : 14-*diazabenz*[d,e]*naphthacene*, is unaffected by boiling acetic anhydride or hot 10% aqueous sodium hydroxide. The presence of a C:N bond rather than a ·CH·NH· system is indicated by analysis and by stability to boiling acetic anhydride.

N-o-*Aminobenzylnaphthalimide*.—*o*-Aminobenzylamine dihydrochloride (2 g.), naphthalic anhydride (2 g.), anhydrous sodium acetate (1·8 g.), and glacial acetic acid (100 ml.) were refluxed for 4 hr. Treatment with water (50 ml.) and 30% sodium hydroxide solution (80 ml.) (cooling) gave an emulsion. After 60 hr. the mustard-coloured precipitate (1·5 g.) (A) was collected and digested with aqueous sodium carbonate on the water-bath to remove unchanged naphthalic anhydride (260 mg.). No pure reaction product was isolated from the carbonate-insoluble precipitate. The acid filtrate from (A) was basified with sodium hydroxide, and a yellow precipitate of N-o-*aminobenzylnaphthalimide* (1·2 g.) separated. After crystallisation from butanol it gave shiny, pale yellow prisms, m. p. 233·5—235° (Found: C, 75·8; H, 4·8; N, 9·1. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·7; N, 9·3%); it is easily diazotised, and coupled with β-naphthol to give a bright red azo-dye. In boiling acetic anhydride it formed a *diacetyl* derivative, pale cream, shiny plates (from ethanol), m. p. 190—191·5° (Found: C, 71·7; H, 4·9; N, 7·6. $C_{23}H_{18}O_4N_2$ requires C, 71·5; H, 4·7; N, 7·3%). The naphthalimide showed considerable resistance to cyclisation, being recovered largely unchanged after being heated to 250°. At 300° it was converted into a dark tar which on chromatography in benzene on alumina gave a complex series of bands from which (VI) separated first and was eluted as a bright yellow solution in benzene. Crystallisation from ethanol gave long, thin, yellow-orange prisms (50 mg. from 250 mg. of the naphthalimide), identified as (VI) by m. p. and mixed m. p.

2′-*Formyldiphenyl*-2-*carboxylic Acid* (I).—The conversion of acid hydrazides into aldehydes by use of potassium ferricyanide and ammonia was studied by Kalb and Gross (*Ber.*, 1926, **59**, 727). Wingfield, Harlan, and Hanmer (*J. Amer. Chem. Soc.*, 1952, **74**, 5796) have shown that, for nicotin hydrazide, at least, sodium metaperiodate is a superior oxidising agent and it is now used for the oxidation of diphenic acid monohydrazide. To a cooled solution of periodic acid (as H_5IO_6; 6 g.) in water (230 ml.) and 8% aqueous ammonia (90 ml.), diphenic acid monohydrazide (6·4 g.) in 8% ammonium hydroxide (40 ml.) was added with vigorous stirring, the temperature being kept at 5—10° (6—8 min.). Stirring was continued for 5 min. longer, gas evolution then having practically ceased. After 15 min. at room temperature the crude product was precipitated (usually as a gum) by acidification with sulphuric acid, and was best purified through the acetyl derivative. After dissolution of the product in acetic anhydride (20 ml.) and concentrated sulphuric acid (10 drops) and 48 hours' standing, the acetyl derivative was separated by stirring the mixture with water (100 ml.), saturated sodium hydrogen carbonate solution (55 ml.), and ethanol (16 ml.) for 3 hr. The product (usually obtained as a gum) was washed well with water, and stirred with ethanol (9 ml.), filtered off, and washed with ethanol (4 ml.) to remove sticky by-products. The white product was crystallised from aqueous ethanol, giving 2·2—2·5 g. of prisms, m. p. 137—138° (lit., 125°) (Found: C, 71·8; H, 4·7. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%). The acetyl derivative (6·7 g.) was hydrolysed by refluxing acetic acid (50 ml.) and 6N-sulphuric acid (50 ml.) for 90 min. After cooling and seeding, the product (5·1 g.) was precipitated with water (120 ml.). Crystallisation from aqueous acetic acid gave small, stout, rectangular prisms, m. p. 135—136° (lit., 132°) (Found: C, 74·2; H, 4·5. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·5%). Simple derivatives of the carbonyl group of (I) do not appear to have been described. The *phenylhydrazone* separated when (I) (56 mg.), phenylhydrazine (3 drops), and 40% acetic acid (2 ml.) were warmed for 10 min. (water-bath). The product (72 mg.) gave, on crystallisation from aqueous ethanol, cream-coloured prisms, m. p. 194—195° (decomp.) (Found: C, 76·2; H, 5·1; N, 9·0. $C_{20}H_{16}O_2N_2$ requires C, 75·9; H, 5·1; N, 8·9%). The *oxime* was formed by refluxing (I) (113 mg.), hydroxylamine hydrochloride (106 mg.), ethanol (10 ml.), and pyridine (2 ml.) for 4 hr., then evaporating the ethanol and adding crushed ice. The product (112 mg.) was precipitated (first as a gum which soon solidified) by just acidifying the solution to Congo-red with dilute hydrochloric acid. Crystallisation from aqueous ethanol gave colourless platelets, m. p. 173·5—174·5° (Found: C, 70·1; H, 4·7; N, 6·1. $C_{14}H_{11}O_3N$ requires C, 69·7; H, 4·6; N, 5·8%). This product dissolves in aqueous sodium hydrogen carbonate solution with effervescence. Under similar conditions *o*-phthalaldehydic acid is converted into hydroxyiminophthalimide (Hatt and Stephenson, *J.*, 1952, 205). (I)

readily gives a positive test with Brady's reagent, and a positive reaction with benzenesulphohydroxamic acid (cf. Feigl, " Qualitative Analysis by Spot Tests," 3rd English edn., transl. by R. Oesper; Elsevier Publ. Co., 1947, p. 346). It does not reduce Fehling's solution.

2 : 2'-Diaminodiphenyl is conveniently prepared from the readily available diphenic acid by a Schmidt reaction (cf. Stephenson, *J.*, 1949, 2620). Sodium azide (11·7 g.) was added portionwise to diphenic acid (9·7 g.) in sulphuric acid (*d* 1·84; 75 ml.) so that the temperature was kept at 30—40° with intermittent cooling (15 min.), and the mixture was then heated at 30—40° (water-bath) for 70 min. It was poured on crushed ice (700 ml.), phenanthridone (1 g.) removed by filtration, and the diamine obtained by basification of the filtrate with sodium hydroxide (120 g.) in water (380 ml.). The crude product was taken up in benzene and chromatographed on a short column of alumina, the diamine being easily eluted with benzene. Crystallisation from aqueous alcohol gave white crystals (4·9 g.), m. p. 81—82°.

When in the above preparation the volume of sulphuric acid was reduced to 20 ml., and 40 ml. of pure chloroform were added, the yield of purified diamine was 1·1 g., and 6·1 g. of phenanthridone was recovered.

I am indebted to Professor W. Davies and Dr. H. H. Hatt for criticism of the manuscript.

UNIVERSITY OF MELBOURNE,
MELBOURNE, AUSTRALIA.

[*Received, February 13th,* 1954.]

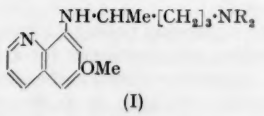
Derivatives of 2-Alkoxy-8-amino-1 : 5-naphthyridines.

By A. A. GOLDBERG, R. S. THEOBALD, and W. WILLIAMSON.

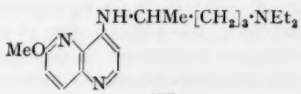
[Reprint Order No. 5165.]

Derivatives of 2-alkoxy-8-amino-1 : 5-naphthyridines have been synthesised for examination for antimalarial activity. The ring system was built up (*a*) by condensation of 5-amino-2-butoxypyridine with ethyl ethoxymethylenemalonate and cyclisation of the product, and (*b*) by condensation of 5-amino-2-butoxypyridine and ethyl acetoacetate by the Conrad–Limpach method.

THE synthesis of 4-dialkylaminoalkylamino-1 : 5-naphthyridines was undertaken because of their structural relationship to 4-dialkylaminoalkylaminoquinolines which have high antiplasmodial activity provided the 6- or the 7-position bears a chloro- or lower alkoxy-substituent (Magidson and Rubtsov, *J. Gen. Chem. Moscow*, 1937, **7**, 1896; Andersag, Breitner, and Jung, G.P. 683,692/1939; Galperin, *Amer. Rev. Soviet Med.*, 1944, **1**, 220). A further point of interest is that pamaquine (I; R = Et) and primaquine (I; R = H) are the most effective of the known antimalarials against the secondary exo-erythrocytic stages of *Plasmodium vivax* (Report by Council on Pharmacy and Chemistry, *J. Amer. Med. Assoc.*, 1952, **149**, 1558); 8-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 5-naphthyridine (II) has a structural contour similar to that of pamaquine inasmuch as the substituted amino-side-chain is *peri* to a ring-nitrogen atom. In the first instance, because of limited availability of starting materials, work was confined to derivatives of 2-alkoxy-8-amino-1 : 5-naphthyridines; synthesis of derivatives of 4-amino-7-chloro-1 : 5-naphthyridines will be reported later.



(I)



(II)

Condensation of 5-amino-2-butoxypyridine with ethyl ethoxymethylenemalonate and cyclisation of the resulting ethyl β-(2-butoxy-5-pyridylamino)-α-ethoxycarbonylacrylate by the method of Price and Roberts (*J. Amer. Chem. Soc.*, 1946, **68**, 1204) gave ethyl 6-butoxy-4-hydroxy-1 : 5-naphthyridine-3-carboxylate. Hydrolysis and decarboxylation of the acid in diphenyl ether afforded 2-butoxy-8-hydroxy-1 : 5-naphthyridine which with phosphoryl chloride yielded the 8-chloro-compound; reaction of the latter at high

temperature with 4-amino-1-diethylaminopentane gave 2-butoxy-8-(4-diethylamino-1-methylbutylamino)-1 : 5-naphthyridine. For the preparation of 8-amino-2-butoxy-1 : 5-naphthyridine it was preferable to convert the chloro- into the phenoxy-compound and treat this in boiling ammonium acetate with ammonia.

Cyclisation of a β-3-pyridylaminoacrylic ester would give a 1 : 5- or a 1 : 7-naphthyridine according as cyclisation occurred at the 2- or the 4-position of the pyridine nucleus. Cyclisation is essentially an attack by a cationoid reagent on the pyridine nucleus and the point of attack will be governed by the relative electron density at the two positions. That the electron density at $C_{(2)}$ is higher than that at $C_{(4)}$ in 3-aminopyridine is shown by chlorination to 2-chloro-3-aminopyridine in 90% yield (Schick, Binz, and Schultz, *Ber.*, 1936, **69**, 2593) and by cyclisation of 2-(6-alkoxy-3-pyridylamino)benzoic acids to 1 : 10-diazaanthracenes (Besly and Goldberg, *J.*, in the press; cf. the Skraup cyclisation with 3-aminopyridine, Klisiecki and Sucharda, *Roczn. Chem.*, 1927, **7**, 204; Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081). There is therefore little doubt that the compounds described in this communication are 1 : 5-naphthyridines.

5-Amino-2-methoxypyridine and ethyl ethoxymethylenemalonate gave similar compounds in good yield, but decarboxylation was difficult. Standard methods yielded unchanged material or effected extensive charring; by heating the silver salt at low pressure, however, 8-hydroxy-2-methoxy-1 : 5-naphthyridine was obtained but the yield was so small that further work was precluded. Condensation of 5-amino-2-methoxypyridine with ethyl ethoxalylacetate in presence of acetic acid and cyclisation of the resulting ethyl β-ethoxycarbonyl-β-(2-methoxy-5-pyridylamino)acrylate yielded ethyl 4-hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylate. Decarboxylation of the corresponding carboxylic acid by standard procedures again presented difficulty but was finally accomplished in refluxing diphenyl ether and dibutyl phthalate. This route was abandoned because of shortage of material.

Condensation of 5-amino-2-methoxypyridine and ethyl acetoacetate by the Conrad–Limpach method gave 4-hydroxy-6-methoxy-2-methyl-1 : 5-naphthyridine. Conversion of this into 4-chloro-6-methoxy-2-methyl-1 : 5-naphthyridine and reaction of the latter with 4-amino-1-diethylaminopentane yielded 4-(4-diethylamino-1-methylbutylamino)-6-methoxy-2-methyl-1 : 5-naphthyridine. The 6-butoxy-analogue was obtained in a similar manner.

2-*n*-Butoxy-8-(4-diethylamino-1-methylbutylamino)-1 : 5-naphthyridine at a daily oral dosage of 40 mg./kg. had the same suppressive activity as 50 mg./kg. of mepacrine against *P. gallinaceum* in chicks; against *P. berghei* in mice, it had the same activity as mepacrine. 6-Methoxy- and 6-*n*-butoxy-4-(4-diethylamino-1-methylbutylamino)-2-methyl-1 : 5-naphthyridine showed no activity against *P. gallinaceum* in chicks at daily oral dosages of 50 mg./kg.

Experimental

Ethyl 6-Butoxy-4-hydroxy-1 : 5-naphthyridine-3-carboxylate.—A mixture of 5-amino-2-*n*-butoxypyridine (Besly and Goldberg, *loc. cit.*; 27 g.) and ethyl ethoxymethylenemalonate (35 g.) was heated for 1 hr. on the steam-bath, the ethanol formed being allowed to escape. The *ethyl β-(2-butoxy-5-pyridylamino)-α-ethoxycarbonylacrylate* (56 g.) solidified on cooling and was pure enough for the cyclisation; a sample crystallised from dilute alcohol in colourless needles, m. p. 54° (Found: N, 8·5. $C_{17}H_{24}O_5N_2$ requires N, 8·3%).

This compound (56 g.) was added during 10 min. to vigorously boiling diphenyl ether (200 g.), the ethanol escaping *via* a short air-condenser. Boiling was continued for a further 15 min., the solution cooled, and *ethyl 6-butoxy-4-hydroxy-1 : 5-naphthyridine-3-carboxylate* [38 g.; m. p. 268° (decomp.)] was precipitated by addition of ligroin (300 c.c.; b. p. 60—80°). Digestion with acetone did not raise the m. p. (Found: C, 62·4; H, 6·4; N, 10·0. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·7%).

2-Butoxy-8-hydroxy-1 : 5-naphthyridine.—The foregoing ester (31 g.) was heated on the water-bath with N-sodium hydroxide (600 c.c.) for 4 hr., and the cooled and filtered (charcoal) solution acidified to Congo-red with hydrochloric acid; the precipitated *acid* (23 g.; m. p. 244°) crystallised from alcohol in colourless needles, m. p. 246° (decomp.) (Found: N, 10·7. $C_{13}H_{14}O_4N_2$ requires N, 10·7%). Adding the acid (23 g.) to refluxing diphenyl ether (50 g.) and,

after 15 min., cooling and adding ligroin (b. p. 60—80°) precipitated 2-*butoxy*-8-*hydroxy*-1 : 5-*naphthyridine* (17·5 g.), m. p. 170°. This crystallised from dilute ethanol in colourless leaflets, m. p. 172° (Found: C, 65·2; H, 6·3; N, 13·0. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·4; N, 12·8%).

2-*Butoxy*-8-*chloro*-1 : 5-*naphthyridine*.—The foregoing compound (17·5 g.) and phosphoryl chloride (50 c.c.) were heated on the steam-bath for 1 hr. and the mixture poured on an excess of crushed ice with vigorous stirring. Sodium acetate was added until the aqueous solution was neutral to Congo-red, and the liquor extracted with ether (500 c.c.). The ether solution was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated; 2-*butoxy*-8-*chloro*-1 : 5-*naphthyridine* (15·1 g.) was obtained as a crystalline mass, m. p. 39°, which crystallised from ligroin (b. p. 40—60°) in colourless prisms, m. p. 40° (Found: N, 11·8; Cl, 14·7. $C_{12}H_{13}ON_2Cl$ requires N, 11·8; Cl, 15·0%).

2-*Butoxy*-8-*phenoxy*-1 : 5-*naphthyridine*.—The foregoing chloro-compound (9 g.) was heated at 160° with a solution of potassium hydroxide (2·2 g.) in phenol (15 g.) for 3 hr.; the solution was cooled and poured into an excess of 2N-sodium hydroxide, and the whole extracted with ether. The ethereal solution was washed several times with dilute aqueous sodium hydroxide, then water, and dried; removal of the ether left 2-*butoxy*-8-*phenoxy*-1 : 5-*naphthyridine* as a light oil (9·5 g.) (Found: N, 9·4. $C_{18}H_{18}O_2N_2$ requires N, 9·5%).

8-*Amino*-2-*butoxy*-1 : 5-*naphthyridine*.—Dry ammonia was passed into a mixture of the foregoing compound (9·5 g.) and ammonium acetate (50 g.) at 150° for 4 hr. The flux was cooled, diluted with water (150 c.c.), and, after addition of acetic acid (10 c.c.), filtered (charcoal) and basified with aqueous ammonia; 8-*amino*-2-*butoxy*-1 : 5-*naphthyridine* (6·7 g.) separated as an oil which rapidly solidified. Crystallisation from ligroin (b. p. 40—60°) gave colourless leaves, m. p. 96—98° (Found: C, 65·9; H, 7·0; N, 19·3. $C_{12}H_{15}ON_3$ requires C, 66·4; H, 6·9; N, 19·4%).

2-*Butoxy*-8-(4-*diethylamino*-1-*methylbutylamino*)-1 : 5-*naphthyridine*.—2-Butoxy-8-chloro-1 : 5-naphthyridine (13 g.), 4-amino-1-diethylaminopentane (44 g.), and copper bronze (2 g.) were heated together at 180—190° for 18 hr. The cooled solution was diluted with 5N-sodium hydroxide and extracted with ether. Distillation of the dried ethereal solution gave a considerable quantity of 4-amino-1-diethylaminopentane and then 2-*butoxy*-8-(4-*diethylamino*-1-*methylbutylamino*)-1 : 5-*naphthyridine* as a colourless oil, b. p. 230—234°/2 mm. (7 g., 30%) (Found: N, 15·8. $C_{21}H_{34}ON_4$ requires N, 15·6%); there was extensive decomposition during the distillation. The *dipicrate* separated from alcohol in yellow leaves, m. p. 170—172° (Found: C, 48·6; H, 4·8; N, 17·2. $C_{21}H_{34}ON_4,2C_6H_3O_7N_3$ requires C, 48·5; H, 4·9; N, 17·2%).

2-*Butoxy*-1 : 5-*naphthyridine*.—2-Butoxy-8-chloro-1 : 5-naphthyridine (5 g.), hydrazine hydrate (25 g., 95%), and ethanol (50 c.c.) were refluxed together for 6 hr., then diluted with water (200 c.c.). The crude hydrazino-compound was collected, washed with water, and suspended in boiling water (50 c.c.), and a concentrated aqueous solution of copper sulphate (10 g.) was added during 5 min. Boiling was continued for 1 hr., and the liquor made alkaline with ammonia and distilled in steam. Ether-extraction of the distillate gave 2-*butoxy*-1 : 5-*naphthyridine* as an oil, b. p. 296—298° (Found: N, 13·9. $C_{12}H_{14}ON_2$ requires N, 13·9%). The *picrate* separated from alcohol in yellow needles, m. p. 135° (Found: N, 16·6. $C_{18}H_{17}O_8N_5$ requires N, 16·2%).

The following were prepared from 5-amino-2-methoxypyridine by the methods described above.

Ethyl β-(2-*methoxy*-5-*pyridylamino*)-α-*ethoxycarbonylacrylate* (85%), colourless leaflets, m. p. 90° (Found: N, 9·7. $C_{14}H_{18}O_5N_2$ requires N, 9·5%).

Ethyl 4-*hydroxy*-6-*methoxy*-1 : 5-*naphthyridine*-3-*carboxylate* (81%), colourless needles (from alcohol), m. p. 268° (decomp.) (Found: C, 57·8; H, 5·0; N, 11·4. $C_{12}H_{12}O_4N_2$ requires C, 58·0; H, 4·8; N, 11·3%). This gave an *acid* (90%), m. p. >310° (decomp.) (Found: N, 12·8. $C_{10}H_8O_4N_2$ requires N, 12·7%). Heating the acid with boiling diphenyl ether or quinoline and copper failed to effect decarboxylation. The silver salt (3·0 g.; prepared by addition of aqueous silver nitrate to an ammoniacal solution of the acid, filtering, and drying at 100°) was heated in a graphite bath to 360—380° (bath-temp.) at 1 mm. for ½ hr. The sublimate and charred residue were extracted with alcohol; evaporation of the solvent and crystallisation of the residue gave 8-*hydroxy*-2-*methoxy*-1 : 5-*naphthyridine* (0·25 g.) in yellow needles, m. p. 270° (Found: N, 15·6. $C_9H_8O_2N_2$ requires N, 15·9%).

Ethyl β-*Ethoxycarbonyl*-β-(2-*methoxy*-5-*pyridylamino*)*acrylate*.—A mixture of 5-amino-2-methoxypyridine (31 g.) and ethyl ethoxalylacetate (31·3 g.) in glacial acetic acid (120 c.c.) was

stirred at 40—50° for 4 hr. and then kept at room temperature overnight. The solution was diluted with water, adjusted to pH 7 with 5N-sodium hydroxide, and extracted with ether. The ethereal solution was washed with 0·5N-hydrochloric acid (4 × 100 c.c.), 0·5N-sodium hydroxide (4 × 100 c.c.), and then water and dried (K_2CO_3); evaporation yielded a residual oil (31 g.). Distillation of a portion gave the pure *ester* as a yellow viscous oil, b. p. 176—180°/1 mm. (Found: N, 9·7. $C_{14}H_{18}O_5N_2$ requires N, 9·5%).

4-Hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylic Acid.—The foregoing crude ester (28 g.) was added during 10 min. to refluxing diphenyl ether (120 g.) down a short air-condenser, thus permitting escape of ethanol. The mixture was refluxed a further 10 min., then cooled, and the precipitate was collected and washed with ligroin (b. p. 60—80°); *ethyl 4-hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylate* remained as a light tan powder (22 g.), m. p. 224—226° (Found: N, 11·2. $C_{12}H_{12}O_4N_2$ requires N, 11·3%). This was heated at 100° for 6 hr. with N-sodium hydroxide (250 c.c.), and the solution made strongly acid with hydrochloric acid; the precipitate of *4-hydroxy-6-methoxy-1 : 5-naphthyridine-2-carboxylic acid hydrochloride* [21 g.; m. p. 270° (decomp.)] was collected and washed with cold alcohol (Found: N, 10·6; Cl, 13·2. $C_{10}H_9O_4N_2Cl$ requires N, 10·9; Cl, 13·8%).

8-Hydroxy-2-methoxy-1 : 5-naphthyridine.—The foregoing hydrochloride (30 g.) was mixed to a paste with dibutyl phthalate and refluxed with diphenyl ether (100 g.) for 20 min. The cooled mixture was filtered, and the solid washed with ligroin and extracted with boiling alcohol. Evaporation of the solvent, and recrystallisation and sublimation of the residue, gave *8-hydroxy-2-methoxy-1 : 5-naphthyridine* (3 g.) (Found: N, 15·0%), m. p. 270° alone and in admixture with a sample made as described above.

4-Hydroxy-6-methoxy-2-methyl-1 : 5-naphthyridine.—Ethyl acetoacetate (36 g.), 5-amino-2-methoxypyridine (34 g.), acetic acid (2 c.c.), and ethyl alcohol (100 c.c.) were refluxed together for 4 hr. Removal of solvent at reduced pressure left almost pure *ethyl β-(2-methoxy-5-pyridylamino)-β-methylacrylate* (67 g.) which crystallised from alcohol in colourless leaves, m. p. 72° (Found: N, 11·9. $C_{12}H_{16}O_3N_2$ requires N, 11·9%).

Cyclisation of this (67 g.) in refluxing diphenyl ether (335 g.) as described above gave *4-hydroxy-6-methoxy-2-methyl-1 : 5-naphthyridine* (42 g.; m. p. 290°) which crystallised from alcohol in colourless needles, m. p. 294—296° (decomp.) (Found: C, 62·9; H, 3·2; N, 14·9. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

The following compounds were obtained by the sequence of reactions described above; the yields and the solvents used for crystallisation are in parentheses.

4-Chloro-6-methoxy-2-methyl-1 : 5-naphthyridine (90%), pale yellow prisms (from ligroin, b. p. 40—60°), m. p. 108° (Found: N, 13·4; Cl, 17·3. $C_{10}H_9ON_2Cl$ requires N, 13·4; Cl, 17·0%).

4-Phenoxy-6-methoxy-2-methyl-1 : 5-naphthyridine (85%), colourless needles (from dilute ethanol), m. p. 114° (Found: N, 10·1. $C_{16}H_{14}O_2N_2$ requires N, 10·5%).

4-Amino-6-methoxy-2-methyl-1 : 5-naphthyridine (58%), colourless needles (from ether–ligroin), m. p. 172° (Found: C, 63·8; H, 5·9; N, 22·4. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8; N, 22·2%).

4-(4-Diethylamino-1-methylbutylamino)-6-methoxy-2-methyl-1 : 5-naphthyridine (40%), a yellow oil, b. p. 220—224°/1 mm. (Found: N, 17·1. $C_{19}H_{30}ON_4$ requires N, 17·0%) [*dipicrate*, yellow aggregates (from acetone), m. p. 148° (decomp.) (Found: C, 47·3; H, 4·4; N, 17·9. $C_{31}H_{36}O_{15}N_{10}$ requires C, 47·2; H, 4·6; N, 17·7%)].

Ethyl β-(2-butoxy-5-pyridylamino)-β-methylacrylate (95%), colourless leaflets (from dilute alcohol), m. p. 55° (Found: N, 10·2. $C_{15}H_{22}O_3N_2$ requires N, 10·1%).

6-Butoxy-4-hydroxy-2-methyl-1 : 5-naphthyridine (78%), colourless needles (from alcohol), m. p. 246° (Found: C, 67·3; H, 7·0; N, 12·3. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

6-Butoxy-4-chloro-2-methyl-1 : 5-naphthyridine (92%), colourless prisms (from ligroin, b. p. 60—80°), m. p. 62° (Found: N, 11·3; Cl, 14·3. $C_{13}H_{15}ON_2Cl$ requires N, 11·2; Cl, 14·2%).

6-Butoxy-2-methyl-4-phenoxy-1 : 5-naphthyridine (85%), colourless needles (from dilute ethanol), m. p. 66—68° (Found: N, 9·2. $C_{19}H_{20}O_2N_2$ requires N, 9·1%).

4-Amino-6-butoxy-2-methyl-1 : 5-naphthyridine (70%), colourless needles (from dilute ethanol), m. p. 142° (Found: C, 67·1; H, 7·4; N, 18·2. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4; N, 18·2%).

6-Butoxy-4-(4-diethylamino-1-methylbutylamino)-2-methyl-1 : 5-naphthyridine (40%), an orange oil, b. p. 230—234°/1 mm. (Found: N, 14·9. $C_{22}H_{36}ON_4$ requires N, 15·0%) [*dioxalate*, nearly colourless needles (from alcohol), m. p. 166° (Found: C, 56·0; H, 7·2; N, 10·3. $C_{26}H_{40}O_9N_4$ requires C, 56·6; H, 7·3; N, 10·2%)].

2-*Butoxy*-6-*methyl*-1 : 5-*naphthyridine monohydrate*, colourless needles, m. p. 56°, very soluble in alcohol and easily sublimed (Found: C, 66·2; H, 8·0; N, 11·9. $C_{13}H_{18}O_2N_2$ requires C, 66·6; H, 7·7; N, 12·0%) [*picrate* (from alcohol), pale yellow needles, m. p. 131° (Found: N, 15·9. $C_{19}H_{19}O_8N_5$ requires N, 15·8%)].

2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine*, colourless needles (after sublimation at 1 mm.), m. p. 52° (Found: C, 68·6; H, 5·6; N, 16·2. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7; N, 16·1%) [*picrate*, yellow needles (from alcohol), m. p. 190° (Found: C, 47·0; H, 3·4; N, 17·6. $C_{16}H_{13}O_8N_5$ requires C, 47·6; H, 3·2; N, 17·4%)].

WARD, BLENKINSOP & CO. LTD., RESEARCH DEPARTMENT,
SHEPTON MALLET, SOMERSET.

[*Received, February 27th*, 1954.]

Studies in the Alicyclic Series. Part I. 1-*Benzoylcycloalkenes as Acceptors in the Michael Condensation.*

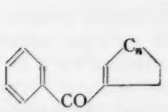
By DAVID GINSBURG.

[Reprint Order No. 5177.]

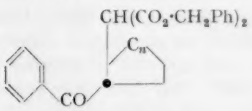
Michael condensation of 1-benzoyl*cyclo*alkenes with benzyl malonate affords products which can be transformed into 2-benzyl*cyclo*alkylacetic acids. The latter can be cyclised to give linear tricyclic substances containing a central seven-membered ring.

THE Michael condensation has been employed extensively for the synthesis of alicylic systems. (A review on "The Michael Condensation" will appear shortly: Bergmann, Ginsburg, and Pappo, "Organic Reactions," Wiley, New York.) In view of our interest in alicylic systems containing seven-membered rings (cf. Ginsburg and Pappo, *J. Amer. Chem. Soc.*, 1953, **75**, 1094) it seemed that tricyclic compounds containing a central seven-membered ring would be readily accessible through Michael condensation of 1-benzoyl-*cyclo*alkenes with suitable hydrogen donors.

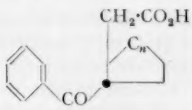
This expectation was realised when three acceptors of this type (I) were treated with benzyl malonate in the presence of potassium *tert.*-butoxide. The corresponding dibenzyl ester adducts (II) were obtained and then hydrogenolysed to give the malonic acids (Ginsburg and Pappo, *loc. cit.*; cf. *J.*, 1953, 1524). Decarboxylation of the latter led to the corresponding 2-benzoyl*cyclo*alkylacetic acids (III).



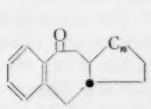
(I; *a*, $n = 1$; *b*, $n = 2$; *c*, $n = 3$)



(II; *a*, $n = 1$; *b*, $n = 2$; *c*, $n = 3$)



(III; *a*, $n = 1$; *b*, $n = 2$; *c*, $n = 3$)



(IV; *a*, $n = 1$; *b*, $n = 2$; *c*, $n = 3$)

Reduction of the keto-acids by Huang-Minlon's procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) led to the corresponding 2-benzyl*cyclo*alkylacetic acids and their respective acid chlorides were treated with aluminium chloride, yielding the tricyclic ketones (IV). In (IV*c*), for example, one has a linear condensed system containing an aromatic ring and two seven-membered rings, isomeric with the angular system and more analogous with that present in colchicine. Certain derivatives of both systems are being prepared for pharmacological evaluation and will be described in a future communication.

The 2-benzyl*cyclo*hexylacetic acid obtained had m. p. 74°. Colonge and Sibeud (*Compt. rend.*, 1952, **234**, 530) described the synthesis of this compound from 2-benzyl*cyclo*hexanone and ethyl chloroacetate, with hydrolysis, dehydration, and Raney-nickel reduction of the unsaturated acid thus obtained; their product had m. p. 58·5°. It has been shown that these are polymorphic forms of the substance and that their infra-red spectra in solution are identical. It appears therefore that in the Raney-nickel reduction the more stable stereochemical possibility is obtained. The semicarbazone of their product

of cyclisation had m. p. 202° upon recrystallisation from ethanol; the similar derivative prepared in this investigation had m. p. 205°. A mixture showed m. p. 204—205°.

Since the 2-benzyl*cyclo*alkylacetic acids are obtained by means of several reactions involving strongly alkaline conditions, it seems reasonable to assign to them the *trans*-configuration. The *trans*-isomer would be diequatorial. The *cis*-isomer would have one substituent in the equatorial, the other in the axial conformation (cf. Barton, *J.*, 1953, 1028). Similar results have been obtained in a study of the Michael condensation of 2-aryl-*cyclo*hex-2-enones (Pappo and Ginsburg, *Bull. Res. Council Israel*, 1951, **1**, No. 3, 121) and of 2-phenyl*cyclo*hept-2-enone (Ginsburg and Pappo, *loc. cit.*). Presumably, therefore, the two alicylic rings in the ketones (IV) are fused in the *trans*-manner.

1-Benzoyl*cyclo*heptene was prepared from benzoyl chloride and *cyclo*heptene in the presence of aluminium chloride. The product was dehydrochlorinated by heating it in dimethylaniline. As this ketone was not previously known, it was necessary to prove that no rearrangement to a *cyclo*hexane derivative had taken place during its preparation by this method. It has been shown that the similar Friedel–Crafts reaction with acetyl chloride must be carried out at low temperature in order to avoid such rearrangement (Fries and Pinson, jun., *J. Amer. Chem. Soc.*, 1951, **73**, 3512; Taub and Szmuszkovicz, *ibid.*, 1952, **74**, 2117). The benzoylation reaction was therefore carried out at −30° to −40° and the resulting product gave a single 2 : 4-dinitrophenylhydrazone, m. p. 132—133°, in high yield, indicating that a mixture of ketones was not present. Furthermore, 1-benzoyl*cyclo*heptene was prepared through the reaction of *cyclo*heptenyl-lithium with benzonitrile, in which the possibility of ring contraction is ruled out. The product was identical in infra-red spectrum and in its 2 : 4-dinitrophenylhydrazone with the ketone and its corresponding derivative prepared by the benzoylation procedure. We learned subsequently (Dr. E. A. Braude, personal communication) that 1-benzoyl*cyclo*heptene has also been prepared by oxidation of the alcohol which results from the reaction of *cyclo*heptenyl-lithium and benzaldehyde. The 2 : 4-dinitrophenylhydrazone of the ketone so prepared had m. p. 133—134° (Braude and Forbes, *J.*, 1953, 2208).

Experimental

1-*Benzoyl*cyclo*pentene*.—This ketone was prepared according to Fuson, Johnson, and Cole (*J. Amer. Chem. Soc.*, 1938, **60**, 1594).

1-*Benzoyl*cyclo*hexene*.—The product was obtained by Christ and Fuson's method (*ibid.*, 1937, **59**, 893).

1-*Benzoyl*cyclo*heptene*.—(*a*) To a mixture of *cyclo*heptene (113 g.), benzoyl chloride (172 g.), and carbon disulphide (400 ml.), small portions of aluminium chloride (176 g.) were added during 3 hr., the temperature being kept at −30° to −40°. Stirring was continued for 2 hr., and the temperature allowed to rise to −10°. No hydrogen chloride was evolved. The mixture was poured into dilute hydrochloric acid containing ice shavings, and the carbon disulphide layer was separated. The solvent was removed under reduced pressure and the residue was refluxed with dimethylaniline for 3 hr. The mixture was cooled, poured into dilute acid, and extracted with chloroform. Fractionation afforded 1-*benzoyl*cyclo*heptene* (130 g.), b. p. 155°/8 mm. (Found: C, 83·5; H, 8·1. $C_{14}H_{16}O$ requires C, 84·0; H, 8·1%). Infra-red absorption: 6·01 μ (C=O). A higher-boiling chlorine-containing fraction (30—40 g.), presumably 1-benzoyl-2-chloro*cyclo*heptane, was also obtained.

The 2 : 4-dinitrophenylhydrazone formed red prismatic needles, m. p. 132—133° (from ethanol–ethyl acetate). Braude and Forbes (*loc. cit.*) report m. p. 133—134°.

(*b*) *Preparation from* cyclo*heptenyl-lithium and benzonitrile*. *cyclo*Heptenyl-lithium was prepared from 1-bromo*cyclo*heptene (8·25 g.) and lithium wire (0·69 g.) in dry ether (100 ml.). To the solution was added benzonitrile (10·3 g.) in dry ether (30 ml.). After refluxing for 4 hr. the mixture was poured into dilute hydrochloric acid. The resulting imine was extracted by the acid, and its solution was refluxed for 3 hr. The solution soon became turbid and drops of ketone were formed in the refluxing solution. After cooling, the ketone was taken up in ether and subsequently purified by distillation. It gave a 2 : 4-dinitrophenylhydrazone, m. p. 132—133°, identical with the one reported above.

Michael Condensations.—The conditions and working-up followed the procedure of Ginsburg and Pappo (*loc. cit.*).

From 1-benzoyl*cyclo*pentene (44·5 g.), benzyl malonate (113 g.), and potassium *tert.*-butoxide (prepared from 3·3 g. of potassium and 50 ml. of *tert.*-butanol), 2-*benzoyl*cyclo*pentylmalonic acid* (34 g.), m. p. 144—145° (decomp.) (from carbon tetrachloride), was obtained (Found: C, 65·4; H, 5·6. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%).

2-*Benzoyl*cyclo*hexylmalonic acid* (25 g.) was similarly obtained from 1-benzoyl*cyclo*hexene (37·2 g.), benzyl malonate (63·9 g.), and the alkoxide prepared from potassium (1·6 g.) and *tert.*-butanol (24 ml.). The acid had m. p. 190—191° (decomp.) (from carbon tetrachloride) (Found: C, 66·4; H, 6·1. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·25%).

2-*Benzoyl*cyclo*heptylmalonic acid* (10·5 g.) was obtained from 1-benzoyl*cyclo*heptene (15 g.), benzyl malonate (42·6 g.), and alkoxide solution prepared from potassium (1 g.) and *tert.*-butanol (15 ml.). It had m. p. 169—170° (decomp.) (from carbon tetrachloride) (Found: C, 67·0; H, 6·4. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

Since all of the 1-benzoyl*cyclo*alkenes were prepared by a Friedel–Crafts reaction in carbon disulphide solution, it is necessary to remove traces of sulphur-containing impurities from the Michael condensation mixtures before hydrogenolysis with palladium–charcoal. This purification is easily effected by refluxing the ethyl acetate solution of the reaction mixture with Raney nickel for 3—4 hr., followed by separation of the Raney nickel.

2-*Benzoyl*cyclo*alkylacetic Acids*.—These acids were obtained through decarboxylation of the corresponding malonic acids at 180—190° for 15—30 min. 2-*Benzoyl*cyclo*pentylacetic acid* was obtained as an oil and purified by evaporative distillation (Found: equiv., 224. $C_{14}H_{16}O_3$ requires equiv., 232·3). Infra-red absorption: 5·78 μ (weak) and 5·89 μ (strong) (monomeric and dimeric CO_2H); 5·97 μ (C=O). 2-*Benzoyl*cyclo*hexylacetic acid* formed prisms, m. p. 103—104° (from carbon tetrachloride) (Found: C, 73·3; H, 7·35. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). Infra-red absorption: 5·89 μ (CO_2H); 5·97 μ (C=O). 2-*Benzoyl*cyclo*heptylacetic acid* was obtained as an oil (Found: equiv., 254. $C_{16}H_{20}O_3$ requires equiv., 260·3). Infra-red absorption: 5·88 μ (CO_2H); 5·97 μ (C=O).

2-*Benzyl*cyclo*alkylacetic Acids*.—These acids were obtained according to Huang-Minlon's method (*loc. cit.*): 2-Benzyl*cyclo*pentylacetic acid, m. p. 53—54° (from light petroleum) [Duff and Ingold (*J.*, 1934, 93) report m. p. 53—54°] (Found: C, 76·8; H, 8·2. Calc. for $C_{14}H_{18}O_2$: C, 77·0; H, 8·3%). 2-Benzyl*cyclo*hexylacetic acid, m. p. 74—75° (from light petroleum). Colonge and Sibeud (*loc. cit.*) report m. p. 58·5°. The infra-red spectra of the polymorphic modifications in carbon tetrachloride solution are identical between 2 and 14 μ. When equal amounts of each form are melted together and allowed to solidify, the m. p. obtained is that of the higher-melting form (Found: C, 77·8; H, 8·5. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·7%). 2-*Benzyl*cyclo*heptylacetic acid* was obtained as an oil which did not crystallise (Found: equiv., 238. $C_{16}H_{22}O_2$ requires equiv., 246·3).

Cyclisation of 2-*Benzyl*cyclo*alkylacetic Acids*.—The acid (0·01 mole) was dissolved in dry benzene (20 ml.) and thionyl chloride (5 ml.) was added. After 2 hours' refluxing evolution of gas was complete. The excess of solvents was removed under reduced pressure. To the residual acid chloride were added carbon disulphide (20 ml.) and aluminium chloride (0·01 mole) in one portion. The mixture was refluxed for 3 hr. and stored overnight. After decomposition with dilute hydrochloric acid and chloroform extraction, the combined organic extracts were distilled under reduced pressure.

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-Octahydro-7-oxo-5 : 6-benzazulene (IV*a*), m. p. 56° (from light petroleum), was obtained from 2-benzyl*cyclo*pentylacetic acid (Found: C, 84·1; H, 8·0. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·05%). Infra-red absorption: 6·01 μ (C=O). The orange 2 : 4-dinitrophenylhydrazone had m. p. 184—185° (from ethanol–ethyl acetate) (Found: C, 63·4; H, 5·2; N, 15·0. Calc. for $C_{20}H_{20}O_4N_4$: C, 63·15; H, 5·3; N, 14·7%). Cook, McGinnis, and Mitchell (*J.*, 1944, 286) report m. p.s 56° and 169—170°, respectively, for these two compounds.

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-Octahydro-7-hydroxy-5 : 6-benzazulene, m. p. 128° (from light petroleum), was obtained by reduction of the above ketone with sodium borohydride in methanol (Found: C, 83·0; H, 9·1. Calc. for $C_{14}H_{18}O$: C, 83·1; H, 9·0%). Cook *et al.* (*loc. cit.*) report m. p. 128—129°

2 : 3 : 12 : 13 : 14 : 15-Hexahydrodibenzosuber-5-one (IV*b*) was obtained as an oil from 2-benzyl*cyclo*hexylacetic acid. Infra-red absorption: 6·03 μ (C=O). The ketone was characterised through its semicarbazone, m. p. 205° (from ethanol) (Found: C, 70·5; H, 7·6; N, 15·6. Calc. for $C_{16}H_{21}ON_3$: C, 70·8; H, 7·8; N, 15·5%). A sample of this compound kindly furnished by Professor J. Colonge had m. p. 202° (from ethanol); mixed m. p., 204—205°.

1 : 4 : 5 : 6 : 7 : 8 : 9 : 10 : 11 : 12-Decahydro-5-oxo-2 : 3-benzoheptalene (IV*c*) was obtained as an oil from 2-benzyl*cyclo*heptylacetic acid. Infra-red absorption 6·03 μ (C=O). It was charac-

terised through its orange 2 : 4-*dinitrophenylhydrazone*, m. p. 227—228° (decomp.) (from ethanol), raised to 229—230° (from ethanol–ethyl acetate) (Found : C, 64·4; H, 6·0; N, 13·5. $C_{22}H_{24}O_4N_4$ requires C, 64·7; H, 5·9; N, 13·7%).

We are grateful to Professor J. Colonge for samples of his specimens. This work was carried out while the author was on leave of absence from the Weizmann Institute of Science during the tenure of a United States Public Health Service post-doctoral fellowship, 1952—1953.

Converse Memorial Laboratory, Harvard University,
Cambridge 38, Mass. [*Received, March 3rd*, 1954.]

Studies on Fructosans. Part V. Short-chain Fructosans from* Lolium perenne.

By V. D. Harwood, R. A. Laidlaw, and R. G. J. Telfer.

[Reprint Order No. 5171.]

A mixture of short-chain fructosans has been isolated from mid-season perennial rye-grass (*Lolium perenne*). On fractionation of the methylated material a product was obtained which, on hydrolysis, yielded 1 : 3 : 4 : 6-tetra- (13·2%) and 1 : 3 : 4-tri-*O*-methyl-D-fructose (76·2%) along with 2 : 3 : 4 : 6-tetra- (5·3%) and 2 : 4 : 6-tri-*O*-methylglucose (4·1%). A di-*O*-methylfructose (1·2%) was also isolated. The findings indicate the presence of short, straight-chain polysaccharides made up of 2 : 6-linked fructofuranose residues, terminated in some cases by a glucopyranose residue linked as in sucrose.

The levans have been studied extensively (see Part IV * and references contained therein; Aspinall and Telfer, *Chem. and Ind.*, 1952, 1244; Bell and Palmer, *J.*, 1952, **3763**), and, while Schlubach and Holzer (*Annalen*, 1953, **578**, 207) have isolated a fructosan from *Lolium perenne* which contained no glucose residues (cf. Laidlaw and Reid, *J.*, 1951, 1830) it seems probable that these polysaccharides occur in the plant as chains of 2 : 6-linked fructofuranose residues some of which, at least, are terminated by a glucopyranose residue linked as in sucrose. This view is in agreement with the theory that fructosans are built up in the plant from sucrose by enzymic transfructosidation. Similar conclusions have been drawn from the results of the present investigation, which had as its object the isolation and investigation of the short-chain " intermediate " levan fractions.

The rye-grass used was oven-dried, milled material prepared from grass cut in May, 1949, at the Jealott's Hill Agricultural Research Station. Extraction with 80% aqueous ethanol gave a mixture of short-chain fructosans. Hydrolysis of the purified material and analysis of the product by paper chromatography (Hirst and Jones, *J.*, 1949, 1659; Duff and Eastwood, *Nature*, 1950, **165**, 848) showed the presence of glucose (8·5%) and fructose (91·5%).

Methylation of the fructosan mixture yielded a product which was fractionated by dissolution in chloroform–light petroleum to give a soluble (64·4%) and an insoluble fraction (35·6%). The fully methylated insoluble fraction (OMe, 47·1%) on hydrolysis yielded 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose (13·2%), 1 : 3 : 4-tri-*O*-methyl-D-fructose (76·2%), 2 : 3 : 4 : 6-tetra-*O*-methylglucose (5·3%), an aldose sugar believed to be probably 2 : 4 : 6-tri-*O*-methylglucose (4·1%), and a di-*O*-methylfructose (1·2%). The tetra- and tri-*O*-methylfructoses were identified as crystalline derivatives. The properties of the aldose—its R_G value, the colour given by aniline oxalate on the chromatogram, the failure to yield a methylfuranoside with cold methanolic hydrogen chloride, and the negative Weerman test given by the derived amide—agreed with those of 2 : 4 : 6-tri-*O*-methylglucose, though we could not, at the time when the experiments were done, prove

* Part IV, Aspinall, Hirst, Percival, and Telfer, *J.*, 1953, 337.

conclusively that this material was, in fact, a derivative of D-glucose. It is to be regretted that no crystalline derivatives of the fully methylated aldose fraction could be obtained, but from paper chromatography and hypoiodite oxidation experiments there would appear to be no doubt of the identity of this fraction. It seems likely that the small amount of di-*O*-methylfructose isolated was an artifact, probably arising from undermethylation.

The proportion of tetra-*O*-methylfructose obtained indicates an average chain length of 7—8 units, while the tetra-*O*-methylglucose content suggests that only one chain in three is terminated by a non-reducing glucose residue, and this accords with the reducing properties of the fructosan and the liberation of formaldehyde on periodate oxidation. It is possible, however, that some degradation of the polysaccharide, with hydrolysis of the sucrose linkage, took place during the preparation of the methylated levan (cf. Part IV, *loc. cit.*).

It cannot be decided on the present evidence whether the tri-*O*-methylglucose found was derived from a 1 : 3-linked glucose unit or whether it was an artifact produced by undermethylation. While previous workers (Hirst, McGilvray, and Percival, Part I, *J.*, 1950, 1297; Bell and Palmer, *loc. cit.*) have reported the isolation of small but significant amounts of 2 : 4 : 6-tri-*O*-methyl-D-glucose from among the products of hydrolysis of methylated inulins, it has been demonstrated by periodate oxidation (Aspinall and Telfer, *Chem. and Ind.*, 1953, 490) that 1 : 3-linked glucose residues were absent from the inulin of " Crimson Flag " dahlia tubers. It was concluded that the tri-*O*-methylglucose isolated in previous experiments must have arisen from undermethylation. Similar considerations may well apply in the levan series. In the present investigation, however, a relatively large proportion of tri-*O*-methylglucose was found, and the quantity of this material, estimated visually on the paper chromatogram after hydrolysis of the methylated fructosan, did not appear to diminish on repeated methylation. It is thus possible that, in this case, 1 : 3-linked glucose may be present. The further question, whether such units, if present, constitute an intrinsic part of the fructosan molecule or whether they are derived from an associated short-chain glucosan, remains unsettled. If the former alternative is correct, these glucose residues may occupy any intermediate position in the fructosan chains, or they may be present as reducing end-groups (cf. the production of a reducing disaccharide, 6-*O*-β-D-fructofuranosyl-D-glucose, by transfructosylation, Whelan and Jones, *Biochem. J.*, 1953, **54**, xxxiv). A structure containing end-groups of this type would give glucose on hydrolysis with invertase, and the reducing glucose unit would be disrupted by periodate oxidation. It is unfortunate that lack of material prevented further examination of the product by these methods.

Hydrolysis of a fully methylated soluble fraction of the fructosan mixture (OMe, 44·4%; $[\alpha]_D^{18}$ +46°) gave a product which furnished very high proportions of tetra- and tri-*O*-methylglucoses. It is likely that considerable degradation of this fraction had taken place during the processes of methylation, etc.

The original fructosan consumed 1·1 mols. of sodium metaperiodate per $C_6H_{10}O_5$ residue, a result in agreement with the conception of a molecule composed of fructofuranose units linked through the 2 : 6-positions. Oxidation with potassium periodate (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27) yielded approximately one mol. of formic acid per seven $C_6H_{10}O_5$ residues. While these results cannot be correlated directly with the methylation data, they may be interpreted as supporting the general conclusions drawn above.

Further evidence of the presence of sucrose residues was afforded by the weakly positive Raybin test given with diazouracil (*J. Amer. Chem. Soc.*, 1933, **55**, 2603; 1937, **59**, 1402).

These results indicate that rye-grass contains a series of levans of low molecular weight. On the basis of their mobilities on the paper chromatogram and from the proportions of tetra-*O*-methylfructose isolated on hydrolysis of the methylated sub-fractions it appears that the fraction studied consisted of a mixture of materials with chain-lengths of *ca.* 5—10 units. It seems likely that the chains are terminated by glucopyranose units, linked as in sucrose, and this is in agreement with the theories advanced by Dedonder (*Compt. rend.*, 1950, **230**, 549, 997; 1951, **231**, 790; **232**, 1134, 1442) and by Bacon and Edelman (*Biochem. J.*, 1951, **48**, 114; **49**, 446, 529; see also MacLeod, *J. Inst. Brew.*, 1953, **59**, 462). The lower members of the rye-grass " fructosan series " have not been investigated as yet.

Experimental

Evaporations were conducted under diminished pressure. Unless otherwise stated, fractions from the cellulose column were evaporated to dryness; solutions of the residues in water were digested with charcoal and filtered hot, then evaporated to dryness; these residues were exhaustively extracted with boiling acetone, and the extracts were evaporated to dryness.

Preparation of the Polysaccharide.—Mid-season perennial rye-grass (oven-dried; 200 g.; cut May 26th, 1949) was extracted with two successive portions of boiling aqueous ethanol (80%; 500 c.c.) for 4 hr. with continuous stirring. The extracts were evaporated to dryness and water (250 c.c.) was added. The mixture was heated to 95°, 0·4N-cadmium sulphate and saturated aqueous barium hydroxide (50 c.c. of each) were added, and the temperature was maintained at 95° for 3 min. (cf. Laidlaw and Reid, *J. Sci. Food Agric.*, 1952, **3**, 19). After cooling and filtration the filtrate was de-ionised by resins (Amberlite IR-4B and IR-100), and the final solution was evaporated to give a syrup.

The combined syrups from 2 kg. of grass were dissolved in water (400 c.c.) and fractionated on a carbon column (120 g. of charcoal + 120 g. of " Filter-Cel ") (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677). After removal of the monosaccharides with water, a further fraction (A; 28·5 g.) was obtained by elution with 40% aqueous ethanol. Fraction A was dissolved in water (200 c.c.), and ethanol (1800 c.c.) was added, to yield a precipitate which was purified by two further precipitations as above. After a further precipitation from 95% ethanol the product was finally obtained as a white powder (6·5 g.) which had $[\alpha]_D^{18}$ −30° (*c*, 1·2 in H_2O) (Found: N, 0·1%). The naphtharesorcinol test for uronic acid was negative. The substance quickly reduced boiling Fehling's solution. The test for sucrose with diazouracil (Raybin, *loc. cit.*) gave a positive result.

Examination on the Paper Chromatogram.—In benzene–pyridine–butanol–water (1 : 3 : 5 : 3) the product remained as a spot on the starting-line, while stachyose travelled *ca.* 10 cm. In *iso*amyl alcohol–pyridine–water (7 : 5 : 7), after prolonged running, the spot moved a very short distance below the starting-line and gave a tail several cm. long, with indications of several discrete spots.

Invertase Hydrolysis.—A concentrated spot of the fructosan was placed on the starting-line of a paper chromatogram and sprayed with 4% (v/v) invertase concentrate (B.D.H.) solution. The paper was suspended over water in an air-oven at 50° for 20 min., and then developed with ethyl acetate–acetic acid–water (6 : 1 : 6). The results indicated the presence of a large amount of apparently unchanged fructosan at the starting-line, a considerable amount of fructose and a small amount of glucose.

Hydrolysis.—The fructosan was hydrolysed at 100° with 3% aqueous oxalic acid (25 c.c.) for 1 hr. (rotation constant). The product on examination on the chromatogram was shown to contain fructose, glucose, and a trace of arabinose. Estimation by the periodate method (Hirst and Jones, *loc. cit.*) gave glucose 8·5% and fructose 91·5%, while the colorimetric Somogyi procedure (Duff and Eastwood, *loc. cit.*) gave glucose 8·4% and fructose 91·6%.

Periodate Oxidation Experiments.—Formic acid. The fructosan was oxidised with potassium periodate (Brown, Halsall, Hirst, and Jones, *loc. cit.*), and the formic acid liberated was determined by titration with 0·01N-sodium hydroxide, *viz.*: 8·9 (24 hr.), 7·6 (48 hr.), 6·9 (96 hr.), 6·7 (144 hr., constant) $C_6H_{10}O_5$ residues per mole of formic acid liberated.

Periodate uptake and formaldehyde production. To the fructosan (*ca.* 0·3 g.) in water (35 c.c.), sodium metaperiodate (15 c.c.; 0·3M) was added. The periodate uptake, determined in 5-c.c. portions by the arsenite method, was 1·05 (30 min.), 1·12 (1 hr., constant) moles of periodate consumed per $C_6H_{10}O_5$ residue.

After one day, 5 c.c. of the solution were withdrawn and the periodate and iodate destroyed by the addition of 1·2M-sodium arsenite (2 c.c.). Aqueous phenylhydrazine hydrochloride (1%; 2 c.c.) and potassium ferricyanide (5%; 1 c.c.) were added, and the solution was acidified with hydrochloric acid, the port-wine colour characteristic of formaldehyde being developed. Cocksfoot-grass levan, on similar treatment, gave no colour (cf. Part IV, *loc. cit.*).

Methylation.—The fructosan (4·6 g.) was methylated under nitrogen at room temperature with methyl sulphate and sodium hydroxide (8 times), then three times with methyl iodide and silver oxide. After each methylation, a small portion of the product was removed and hydrolysed, and the sugars were examined on the chromatogram. After the first few methylations, no appreciable change in the amount of tri-*O*-methylglucose present could be detected. The product was dissolved in chloroform (75 c.c.), and the solution dried (Na_2SO_4) and poured into light petroleum (b. p. 60—80°; 750 c.c.), to give a precipitate X (1·44 g.). Evaporation of the filtrate yielded a syrup Y (2·61 g.).

Precipitate X.—Hydrolysis of X and fractionation of the sugars. Fraction X {OMe, 47·1%; $[\alpha]_D^{20}$ −60° (*c*, 0·86 in $CHCl_3$); properties unchanged on further methylation} (*ca.* 1 g.) was heated with methanol (100 c.c.) and water (33 c.c.) containing oxalic acid (1·35 g.) at 80° for 24 hr. The solution was filtered, water (300 c.c.) was added, and the methanol–water mixture was removed by evaporation to small volume. The aqueous solution (150 c.c.) was heated at 80° for 5 hr. Neutralisation, evaporation to small volume, extraction of the residue with acetone, and evaporation of the extracts almost to dryness yielded a thin syrup which was fractionated on a column of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) with benzene–ethanol–water (169 : 47 : 15) (Andrews, Hough, and Jones, *J.*, 1952, 2746) as solvent, to give fractions (1)—(7).

In investigations of the fractions by paper chromatography two solvent systems were used. These were benzene–ethanol–water (as above) (A) and butanol–ethanol–water–ammonia (40 : 10 : 49 : 1) (B). Solvent A had previously been shown to separate 1 : 3 : 4 : 6-tetra-*O*-methylfructose, 2 : 3 : 4 : 6-tetra-*O*-methylglucose, 1 : 3 : 4-tri-*O*-methylfructose, and 2 : 3 : 4- and 2 : 4 : 6-tri-*O*-methylglucoses (R_G values *ca.* 1·14, 1·00, 0·66, 0·40, and 0·32 respectively in this solvent). All chromatograms were run in the presence of authentic specimens of the appropriate sugars.

Because of the high volatility of tetra-*O*-methylfructofuranose at reduced pressures, solutions containing this material were never evaporated to dryness before the weight of the sugar present had been determined. The estimation was carried out on an aliquot portion in aqueous solution by the resorcinol method (Bell and Palmer, *J.*, 1949, 2522; Arni and Percival, *J.*, 1951, 1822). It seems unlikely, in view of Bell and Palmer's findings (*J.*, 1952, 3763), that any appreciable amounts of contaminating non-reducing materials were present in these fractions.

Fraction (1), on investigation by paper chromatography, was shown to contain only 1 : 3 : 4 : 6-tetra-*O*-methylfructofuranose and estimation by resorcinol indicated the presence of 91·5 mg. of this sugar in (1). The material was identified by conversion into tetra-*O*-methyl D-fructofuronamide (Avery, Haworth, and Hirst, *J.*, 1927, 2313), m. p. and mixed m. p. 101° (Found: OMe, 48·5. Calc. for $C_{10}H_{19}O_6N$: OMe, 49·8%).

Fraction (2) was shown by paper-chromatography to be a mixture of tetra-*O*-methylglucopyranose and tetra-*O*-methylfructofuranose. The tetra-*O*-methylfructose content, estimated as above on a portion of the fraction, was 31·5 mg. The remainder of the fraction was evaporated to dryness. Hypoiodite oxidation (Part I, *loc. cit.*) of the resulting syrup indicated the presence of 25·3 mg. of tetra-*O*-methylaldose in fraction (2).

Fraction (3) (24 mg.) gave one spot on the chromatogram corresponding to tetra-*O*-methylglucose. Hypoiodite oxidation indicated 91% purity. Attempts to prepare crystalline derivatives from this fraction were unsuccessful.

Fraction (4) (651 mg.) crystallised completely. Chromatographic examination indicated the presence of 1 : 3 : 4-tri-*O*-methyl-D-fructose and no aldose. After recrystallisation from carbon tetrachloride–light petroleum, 1 : 3 : 4-tri-*O*-methyl-D-fructose, m. p. and mixed m. p. 74°, $[\alpha]_D^{18}$ −45° (10 min.), −53° (1 hr., constant) (*c*, 1·96 in H_2O), was obtained (Found: OMe, 40·9. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction (5) (82·2 mg.) was shown by chromatography to contain tri-*O*-methylfructose and an aldose derivative along with traces of more fully methylated materials. Hypoiodite oxidation indicated the presence of 24·7 mg. of tri-*O*-methylaldohexose. Fraction (5) was separated into its components by partition on Whatman's 3MM paper.

Fraction (6) (13·7 mg.) was shown by chromatography and by hypoiodite oxidation to consist almost entirely of an aldose, and the fraction was combined with the aldose isolated from (5). The combined fraction had the same R_G value as 2 : 4 : 6-tri-*O*-methylglucose. The syrup (15·6 mg.) in 1% methanolic hydrogen chloride showed $[\alpha]_D^{18}$ +70°, unchanged in 24 hr. The syrup was recovered from the polarimetric solution and converted *via* the lactone into the syrupy amide, which gave a negative Weerman test.

Fraction (7) (10·8 mg.) had an R_G value corresponding to that of 3 : 4-di-*O*-methylfructose and was not further investigated.

Syrup Y.—Further methylation of the syrup Y with silver oxide and methyl iodide gave a product which was dissolved in chloroform (20 c.c.). Light petroleum (750 c.c.) was added and the precipitate (0·45 g.) which formed was removed by filtration. This material presumably consisted of fructosans of a molecular size intermediate between those of precipitate X and the soluble fraction, but was not further investigated. Evaporation of the filtrate yielded a syrup (1·93 g.) which was dissolved in ether and added to excess of light petroleum. The black precipitate was filtered off and the filtrate was evaporated to a syrup (1·42 g.) (Found: OMe,

44·4%). Further methylation did not increase the methoxyl content. The product showed $[\alpha]_D^{18}$ +46° (*c*, 0·35 in $CHCl_3$).

The syrup was hydrolysed under the conditions used for precipitate X, and a portion (0·39 g.) was fractionated on a column of cellulose. The amounts of the component sugars were estimated as detailed above and were: tetra-*O*-methylglucose, 59·4 mg.; tetra-*O*-methylfructose, 63·8 mg.; tri-*O*-methylglucose, 64·4 mg.; tri-*O*-methylfructose, 73·8 mg. No di-*O*-methyl sugars could be detected.

The authors thank Professor E. L. Hirst, F.R.S., for his interest and advice. This work forms part of a series of investigations on the composition of grasses and silage, sponsored in part by the Agricultural Research Council, and in part by Imperial Chemical Industries Limited, Central Agricultural Control.

Department of Chemistry, University of Edinburgh. [*Received, March 1st*, 1954.]

Investigations on the Co-ordinative Power of Uranyl. Part I. The Preparation and Properties of Uranyl Complexes of Certain β-Diketones.

By L. Sacconi and (Miss) G. Giannoni.

[Reprint Order No. 5104.]

Uranyl acetate and nitrate, with some β-diketones, yield a series of complexes of different composition. The constitution of the complexes, their solubilities, and their behaviour toward different reagents show that uranium(VI), bound to six oxygen atoms, is co-ordinatively unsaturated. The properties of some water-insoluble and undissociated nitrato-complexes afford conclusive evidence of the existence of covalent bonds between uranyl and nitrate ions. A polymer complex of benzoylnicotinoylmethane is believed to be an instance of 8-co-ordination around uranium(VI).

During recent work on uranyl compounds knowledge has accumulated on the singular properties of uranyl nitrate (cf. Glueckauf and McKay, *Nature*, 1950, **165**, 594; Irving, *Quart. Reviews*, 1951, **5**, 208). This compound is easily soluble in organic solvents containing oxygen atoms capable of electron donation (Guempell, *Bull. Soc. chim. Belg.*, 1929, **38**, 443; Misciatelli, *Gazzetta*, 1930, **60**, 839) and its partition coefficient between water and ethyl ether is very high (Katzin and Sullivan, *J. Phys. Coll. Chem.*, 1951, **55**, 346). Uranyl nitrate, dissolved in such organic solvents, forms a series of hydrates, being associated, on an average, with four water molecules (Katzin and Sullivan, *loc. cit.*; McKay and Mathieson, *Trans. Faraday Soc.*, 1951, **47**, 428; Glueckauf, McKay, and Mathieson, *ibid.*, p. 437; Gardner, McKay, and Warren, *ibid.*, 1952, **48**, 997; Katzin, Simon, and Ferraro, *J. Amer. Chem. Soc.*, 1952, **74**, 1191). Solid compounds which are most often of the formula $UO_2(NO_3)_2,2H_2O,2S$, $UO_2(NO_3)_2,3H_2O,S$, where S is a solvent organic molecule, have been isolated (Mathieson, *J.*, 1949, S294; Katzin and Sullivan, *loc. cit.*). Evidence of the existence of the ion $[UO_2(NO_3)_3]^-$ (Kaplan, Hildebrandt, and Ader, ANL, 1950, 4520, 4521; Jander and Wendt, *Z. anorg. Chem.*, 1949, **258**, 1) and the features of the spectrum of $[UO_2(NO_3)]^+$ (Betts and Michels, *J.*, 1949, S286) have suggested formation of covalent, rather than ionic, bonds between uranyl and nitrate ions (cf. Glueckauf and McKay, *loc. cit.*; Irving, *loc. cit.*).

On the basis of these experimental data which have led to the assumption of an 8-co-ordination involving ten electron orbitals in the complex $[UO_2(H_2O)_4(NO_3)_2]$, Glueckauf and McKay (*loc. cit.*) have advanced the hypothesis that uranyl nitrate forms covalent complexes possibly involving 5*f*-orbitals.

Although Katzin (*Nature*, 1950, **166**, 605) denies that covalent bonds can exist between uranyl and nitrate groups, and therefore deems such an assumption unnecessary, Seaborg and Street (*J. Amer. Chem. Soc.*, 1950, **72**, 2790), Seaborg, Street, and Diamond (quoted in "Comprehensive Inorganic Chemistry," The Actinide Series, Seaborg, Van Nostrand

Company, Inc., New York, 1953, p. 168), and Connick and Hugus (*J. Amer. Chem. Soc.*, 1952, **74**, 6012) favour the suggestion of possible *f*-shell covalency.

To obtain information on this matter, we have investigated the complexing behaviour and co-ordinative power of the uranyl ion, and have studied the behaviour of uranyl acetate and nitrate with certain β-diketones, and the properties of the compounds so obtained.

Some complexes of uranyl and β-diketones have been described, namely, those with acetylacetone (Biltz, *Z. anorg. Chem.*, 1904, **40**, 221), and with ammonia, acetylacetone, and pyridine (Hager, *ibid.*, 1927, **162**, 85). We have considered the following β-diketones (generalised as "diketH"): benzoylacetone (benzacH), dibenzoylmethane (dimetH), picolinoylacetone (picacH), benzoylpicolinoylmethane (picmetH), nicotinoylacetone (nicacH), benzoylnicotinoylmethane (nicmetH), benzoylfuroylmethane (furmetH), 5-acetoacetyl-3-methyl*iso*oxazole (isoxacH), 5-benzoylacetyl-3-methyl*iso*oxazole (isoxmetH).

In aqueous alcohol, uranyl acetate, with all the above β-diketones except benzoylnicotinoylmethane, forms a series of complexes which crystallise with water and are more or less intensely orange. Their general formula corresponds to $UO_2(diket)_2,nH_2O$, where n varies from 1 to 2·8. The water is strongly bound and is eliminated only with difficulty over phosphoric oxide at 95—100° under 0·01 mm., the colour of the compounds then becoming generally red or brownish-red. On the other hand, benzoylnicotinoylmethane, with uranyl acetate, forms an anhydrous compound of approximate constitution $UO_2(nicmet)_2$ having very different properties (see p. 2370). By mixing aqueous solutions of uranyl nitrate with alcoholic solutions of benzoylpicolinoylmethane and benzoylnicotinoylmethane, compounds of the formulæ $UO_2(picmetH)_2(NO_3)_2$ and $UO_2(nicmetH)_2(NO_3)_2$, respectively, are formed. The picolinoyl compound can be obtained also by treating the complex $UO_2(picmet)_2,2{\cdot}5H_2O$ with nitric acid in aqueous alcohol. Both these nitrates, which are orange, behave as true complexes.

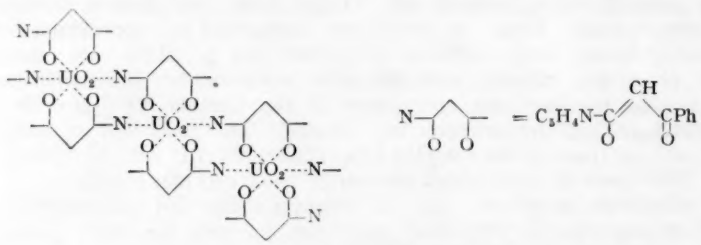
The anhydrous complexes, *e.g.*, of benzoylacetone and dibenzoylmethane, when dissolved or suspended in anhydrous ether, combine with the ether, giving crystalline, yellowish-orange compounds. By addition of anhydrous ammonia or pyridine, compounds of the formulæ $UO_2(benzac)_2,NH_3$, $UO_2(benzac)_2,C_5H_5N$, $UO_2(dimet)_2,NH_3$, and $UO_2(dimet)_2,C_5H_5N$ are formed.

The complexes of the type $UO_2(diket)_2,nH_2O$ are soluble only (or almost solely) in organic solvents containing oxygen atoms capable of electron donation, namely, methyl and ethyl alcohol, acetone, ethyl ether (especially if the last is water-saturated). They are sparingly soluble or insoluble in carbon tetrachloride and carbon disulphide. This behaviour leads to the assumption, which agrees with Martell and Calvin's general views (cf. "Chemistry of the Metal Chelate Compounds," Prentice-Hall Inc., New York, 1952, p. 243), that interaction between solvent and solute occurs by direct co-ordination of the solvent molecules to the central metal atom, rather than by polar interaction or hydrogen bonding between solvent molecules and the attached groups. This fact indicates a co-ordinative unsaturation of the uranium central atom; and, since in the uranyl–diketone complexes uranium(VI) is co-ordinatively bound to six oxygen atoms, we must conclude that in these compounds uranium(VI) shows a co-ordination number greater than 6. This view is supported by the behaviour of some uranium(IV) complexes of β-diketones of the formula $U(diket)_4$ described by Sacconi (*R. Accad. Lincei*, 1949, [8], **6**, 639), which show solubility properties opposite to those of uranyl diketone complexes. They are, in fact, extremely soluble in carbon tetrachloride, carbon disulphide, and benzene, very sparingly soluble in alcohol and ether. As in these complexes uranium(IV), according to magnetic measurements, is 8-covalent (Sacconi, *loc. cit.*; cf. Martell and Calvin, *op. cit.*, pp. 240, 243, 248, 325, 463, etc.) and therefore co-ordinatively saturated, the absence of interactions between the U(IV)–diketone complexes and the molecules of the oxygen-containing solvent supports the conclusion that the solvent molecules containing donor atoms are bound to the uranyl complexes by direct co-ordination to the U(VI) central atom.

The compounds $UO_2(picmetH)_2(NO_3)_2$ and $UO_2(nicmetH)_2(NO_3)_2$ also show a marked tendency to solvation and hydration: indeed, they are soluble only in solvents such as alcohol, acetone, and water-saturated ethyl ether. Evidently, as assumed for uranyl

nitrate (Glueckauf, McKay, and Mathieson, *loc. cit.*; Glueckauf and McKay, *Nature*, *loc. cit.*), the uranium central atom co-ordinates by preference to water which forms, in this way, a " primary " solvation shell, to which the solvent molecules adhere through oxygen–hydrogen bonds (cf. Bockris, *Quart. Reviews*, **1949**, **3**, 174). Because of their properties both these complexes can be classified as non-electrolytes: indeed, their electrical conductivity in aqueous ethyl ether is negligible, like that of the inner complexes $UO_2(dimet)_2,2{\cdot}5H_2O$, etc. This behaviour affords decisive evidence of the existence of covalent bonds between uranium(VI) and nitrate ions. Both the above-mentioned compounds can be considered as complex entities, $[UO_2(picmetH)_2(NO_3)_2]$ and $[UO_2(nicmetH)_2(NO_3)_2]$, respectively.

The constitution and properties of the compound corresponding to the formula $UO_2(nicmet)_2$ strongly support the conclusion that, in this complex, uranium(VI) shows a co-ordination number greater than 6. Indeed, in agreement with previous studies (Jensen, *Z. anorg. Chem.*, **1944**, **252**, 227; Hieber and Brück, *ibid.*, 1952, **269**, 14; Sacconi, *ibid.*, 1953, **271**, 176), the insolubility of this compound in inert organic solvents, its amorphous appearance, and its high thermal stability (at 350° it neither melts nor decomposes) can be interpreted as related to a polymer polynuclear structure of the type shown below.



A structure of such a type implies the 8-co-ordination of the uranium(VI). Moreover, it explains the absence of water in the compound as well as its insolubility in all undissociating solvents. Indeed, it is conceivable that the central uranium atom, being co-ordinatively saturated, will have no capacity to attract molecules of water or oxygenated solvents. Moreover, the solvents such as carbon tetrachloride, carbon disulphide, etc., though they are capable of strong interactions with the groups attached to the uranium, are not able to dissolve the compound on account of its polymeric nature. It can be dissolved only by pyridine, probably through a breaking of the polymer chain and subsequent co-ordination of the pyridinic nitrogen atom to the uranium central atom. The formation of polymer polynuclear complexes including intermolecular co-ordinative bonds from the nitrogen atoms of the nicotinoyl groups has been already demonstrated in the case of some nickel hydrazide complexes (Sacconi, *Gazzetta*, 1953, **83**, 894; *Z. anorg. Chem.*, 1954, **275**, 249). No hypothesis can be advanced about the structure of the 8-co-ordinate bonds in the polynuclear complex. One should remember, however, the arrangement of six coplanar links around the uranium(VI) revealed in the double nitrate $Rb[UO_2(NO_3)_3]$ (Hoard and Stroupe, quoted in " Spectroscopic Properties of Uranium Compounds," by Dieke and Duncan, McGraw-Hill, New York, 1949, p. 15; cf. Glueckauf and McKay, *loc. cit.*).

Experimental

Known β-diketones were prepared according to recorded methods (see Sacconi, *R. Accad. Lincei, loc. cit.*). Picolinoylacetone was mentioned by Van Uitert, Fernelius, and Douglas (*J. Amer. Chem. Soc.*, **1953**, **75**, 458), but its preparation has not been described.

Picolinoylacetone.—Sodium (2·3 g.) was added to a mixture of ethyl picolinate (15 g.), dried acetone (5·8 g.), and anhydrous ethyl ether (50 c.c.) during 20 min. under reflux. The reaction was controlled initially by cooling in ice. After 3 hr., the mixture was warmed at *ca.* 40° for 30 min. The ochre-yellowish sodium salt of the β-diketone was collected, washed with anhydrous ether, dried, and then added in portions to dilute ice-cooled acetic acid (60 c.c.).

Crystallisation from ethanol–water (charcoal) yielded picolinoylacetone as ivory crystals, m. p. 48—50° (yield 40%) (Found: N, 8·56. Calc. for $C_9H_9O_2N$: N, 8·59%).

Benzoylpicolinoylmethane.—After addition of sodium (2·3 g.) to ethyl picolinate (15 g.) and acetophenone (12 g.) in anhydrous ether (100 c.c.), subsequent treatment analogous to that above yielded *benzoylpicolinoylmethane* as ivory crystals (50%), m. p. 87—88° (Found: N, 6·26. $C_{14}H_{11}O_2N$ requires N, 6·22%).

Hydrated uranyl–diketone complexes were obtained by mixing an aqueous solution of uranyl acetate dihydrate (1 mol.) with an alcoholic solution of the β-diketone (2 mol.). Immediately, or after short heating on the steam-bath, crystalline products were precipitated and were recrystallized from alcohol. Samples for analysis were dried (H_2SO_4 *in vac.*) to constant weight. The compounds were analyzed by conversion into U_3O_8 and weighing. The water content was obtained by dehydration at 100°/0·01 mm. over phosphoric oxide to constant weight.

In the Table, Nos. 1—8 give the results obtained for such compounds, and Nos. 9—15 those for the seven complexes whose preparations are reported below.

(9) *Uranyl–benzoylacetone complex–ammonia.* Dry ammonia is passed through a suspension of the complex 1 (0·7 g.) in anhydrous ether (50 c.c.). Dissolution soon takes place and a yellow precipitate of tabular crystals is formed.

(10) *Uranyl–benzoylacetone complex–pyridine* (A different method of preparing this compound is reported by Hager, *loc. cit.*). Pyridine (4 c.c.) is added to a solution of the complex 1 (1·5 g.) in methyl alcohol (100 c.c.), and the mixture heated on the steam-bath for 1 hr., giving an orange precipitate.

			Analysis									
			Found, %					Required, %				
No.	Uranyl complexes	Behaviour on heating	C	H	N	U	H_2O	C	H	N	U	H_2O
1	$UO_2(benzac)_2,2{\cdot}5H_2O$	A	37·45	3·72	—	37·35	—	37·68	3·63	—	37·34	—
2	$UO_2(picac)_2,1H_2O$	B	—	—	4·51	38·78	—	—	—	4·57	38·87	—
3	$UO_2(nicac)_2,2H_2O$	C	—	—	4·76	37·95	5·70	—	—	4·45	37·79	5·68
4	$UO_2(isoxac)_2,2{\cdot}5H_2O$	D	—	—	4·23	36·74	—	—	—	4·33	36·74	—
5	$UO_2(dimet)_2,2{\cdot}5H_2O$	E	47·78	3·41	—	31·20	5·90	47·31	3·57	—	31·26	5·91
6	$UO_2(picmet)_2,2{\cdot}5H_2O$	F	—	—	3·88	31·04	—	—	—	3·67	31·18	—
7	$UO_2(furmet)_2,2{\cdot}2H_2O$	G	42·57	3·15	—	32·31	—	42·42	3·07	—	32·34	—
8	$UO_2(isoxmet)_2,2{\cdot}8H_2O$	H	—	—	3·59	30·63	—	—	—	3·60	30·65	—
9	$UO_2(benzac)_2,NH_3$	I	—	—	2·32	39·67	—	—	—	2·30	39·06	—
10	$UO_2(benzac)_2,C_5H_5N$	J	—	—	2·13	35·35	—	—	—	2·08	35·45	—
11	$UO_2(dimet)_2,NH_3$	K	—	—	1·89	32·63	—	—	—	1·91	32·45	—
12	$UO_2(dimet)_2,C_5H_5N$	L	—	—	1·86	30·09	—	—	—	1·76	29·92	—
13	$UO_2(picmetH)_2(NO_3)_2$	M	39·79	2·56	6·66	28·06	—	39·82	2·62	6·63	28·19	—
14	$UO_2(nicmetH)_2(NO_3)_2$	N	39·95	2·64	6·70	28·73	—	39·82	2·62	6·63	28·19	—
15	$[UO_2(nicmet)_2]_x$	O	—	—	3·92	33·40	—	—	—	3·90	33·15	—

A, Above 120° turns red; at 258—259° melts. B, Decomp. at 182—183°. C, Does not melt at 270°. D, Decomposes at 190—205°. E, Above 140° turns red; melts at 267—271° (decomp.). F, Above 215° decomp. G, Above 150° decomp. H, Neither melts nor decomposes at 280°. I, Above 120° darkens to red; melts at 162—164° (decomp.). J, Melts at 242—243° (decomp.). K, Above 140° darkens to red; decomp. at 215°. L, Melts between 235° and 245° (decomp.). M, Decomp. above 170°. N, Decomp. at 210°. O, Neither melts nor decomposes at 350°.

(11) *Uranyl–dibenzoylmethane complex–ammonia.* Dry ammonia is bubbled through a solution of the complex 5 (1·2 g.) in anhydrous ether (100 c.c.). A crystalline precipitate is formed.

(12) *Uranyl–dibenzoylmethane complex–pyridine.* Dry pyridine (4 c.c.) is added to a solution of the complex 5 (1·5 g.) in anhydrous ether (100 c.c.). A crystalline precipitate is suddenly formed.

(13) *Nitrate of uranyl–benzoylnicotinoylmethane complex.* A solution of uranyl nitrate hexahydrate (1 g.) in water (7 c.c.) is mixed with a solution of benzoylnicotinoylmethane (1·1 g.) in alcohol (20 c.c.). The intensely orange precipitate is recrystallized from alcohol.

(14) *Nitrate of uranyl–benzoylpicolinoylmethane complex.* A solution of uranyl acetate dihydrate (1 g.) in water (10 c.c.) is mixed with a solution of benzoylpicolinoylmethane (1 g.) in alcohol (40 c.c.). The precipitate so formed is dissolved by heat and addition of a few c.c. of concentrated nitric acid and alcohol (50 c.c.). On cooling, an orange crystalline precipitate is formed. It can also be prepared as for No. 13.

(15) *Uranyl–benzoylnicotinoylmethane complex.* A solution of uranyl acetate (1 g.) in water

(10 c.c.) is mixed with a solution of benzoylnicotinoylmethane (1 g.) in alcohol (50 c.c.). After short heating on the steam-bath, the amorphous yellowish-orange precipitate formed is filtered off. It is insoluble in water and in all inert organic solvents, but sparingly soluble in pyridine.

Thanks are expressed to the Accademia dei Lincei for a grant to one of us (G. G.). The financial assistance of the Italian Research Council (C. N. R.) which supported this research is acknowledged.

Istituto di Chimica Fisica dell' Università di Firenze,
Via G. Capponi, 9, Florence. [*Received, February 8th,* 1954.]

The Amination of Anthraquinone with Hydroxylamine in Sulphuric Acid.

By A. C. Robson and Samuel Coffey.

[Reprint Order No. 5120.]

This reaction affords a mixture of 1- and 2-amino- and 1 : 4-, 1 : 5-, 1 : 6-, 1 : 7-, 1 : 8-, and 2 : 7-diamino-anthraquinone. Substitution occurs equally in the α- or the β-positions.

The direct amination of aromatic compounds with hydroxylamine in concentrated sulphuric acid catalysed by ferrous sulphate was first described by Turski (G.P. 287,756), who claimed that 1-aminoanthraquinone could be isolated from the product, although Kniatowna (*Bull. Soc. chim.*, 1924, **35**, 207) found that this was not easy. Subsequently, a vanadium catalyst was used as an alternative and the hydroxylamine was produced *in situ* from a nitroparaffin (Turski, B.P. 564,610; 626,661). Separation and identification of the principal products has now been achieved by chromatography on very active alumina. Since the present work was carried out (in 1944), Rao, Shah, and Venkataraman (*Proc. Indian Acad. Sci.*, 1951, **34**, 354) and Hoyer (*Kolloid Z.*, 1951, **121**, 121) described the qualitative behaviour of individual aminoanthraquinones and selected two-component mixtures on alumina with benzene or methylene chloride as solvent, but there is no record of quantitative chromatographic examination of a complex mixture.

A two-stage chromatographic procedure, supplemented by fractional crystallisation (see Experimental section) was worked out which effectively separated the nine components in the product. The results (see Table) show that the reaction is far more complicated than was originally suspected. Not only is 1-aminoanthraquinone formed but also at least an equal amount of 2-aminoanthraquinone, and both compounds are aminated further to produce diaminoanthraquinones. Apart from the very small amount of 1 : 4-diaminoanthraquinone produced when a vanadium catalyst is used, all the diaminoanthraquinones have the two substituents in different rings. Vanadium is a more active catalyst than ferrous iron, but the reaction takes a similar course. The reaction still occurs, though much more slowly, in sulphuric acid containing no added catalyst. No special precautions were taken to use specially purified sulphuric acid but the amount of iron and other metals present in that used was extremely small.

The mechanism of amination is still obscure. Some suggestions have been made, for example by Keller and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 1122), that the active agent is the NH_2^+ ion but the most recent text-books on chemical kinetics and the mechanism of reactions say nothing on the matter. Our results for anthraquinone indicate that, whatever the reactive species may be, it produces random substitution, α- and β-positions being attacked with equal facility.

Experimental

Amination of Anthraquinone.—(*a*) *With an iron catalyst.* Ferrous sulphate crystals (0·9 g.) were dissolved in 90% sulphuric acid (120 g.), and anthraquinone (10 g.) followed by hydroxylamine sulphate (9 g., 1·17 equiv. of NH_2·OH) was added to the stirred solution. The addition of the latter caused the precipitation of anthraquinone but it re-dissolved on warming to 100—

110°. The temperature was raised to 160° during 45 min. and kept at 160—165° for 4 hr. After cooling to 80° the mixture was poured into ice and water, and the product filtered off, washed with dilute aqueous ammonia, and dried (yield 10·48 g.). The crude product was extracted (Soxhlet) with chlorobenzene (2·5 l.), and the insoluble residue discarded. On cooling, the extract deposited reddish crystals (2·8 g.), m. p. *ca.* 298°, which were filtered off and examined separately. The chlorobenzene solution was passed through a column (24 × 2″) containing activated alumina (Type " O " as supplied by Peter Spence & Sons Ltd., Widnes) under slight pressure (4″ water). The column was developed with chlorobenzene containing 5% of pyridine, bands being developed as shown in the Table, and separated with the same solvents. The amines, recovered by removal of the solvent (the last traces by steam), crystallised from an appropriate solvent, and were converted into acetyl and benzoyl derivatives and identified by comparison with authentic specimens.

A portion (1 g.) of the small fraction which crystallised from the original solution in chlorobenzene was dissovled in pyridine (50 c.c.), and the solution diluted with chlorobenzene (150 c.c.), then chromatographed on alumina (12 × 1″) with the same mixed solvent, giving mainly 2-amino-, 1 : 7- and 2 : 7-diamino-, and traces of 1-amino- and 1 : 6-diamino-anthraquinones.

The combined yields of the individual amines isolated are given in the Table. The compounds bracketed together were separated as one band and identified as shown later.

(*b*) *With a vanadium catalyst.* A similar experiment in which vanadium pentoxide (0·3 g.) was used instead of ferrous sulphate gave 10·75 g. of product, which was extracted with chlorobenzene, giving 0·65 g. of insoluble matter (discarded), a crystalline less-soluble fraction, subsequently chromatographed separately (1·45 g.), and a solution which was chromatographed as described above.

The combined yields are also given in the Table.

		$FeSO_4$ catalyst		V catalyst		
Order of elution	Colour of band	Yield (g.)	M. p. (crude)	Yield (g.)	M. p. (crude)	M. p. (pure)
Anthraquinone	Pale yellow	3·7	281°	2·75	—	284°
1-Amino-anthraquinone ...	Orange-red	1·45	245	1·82	247—249°	251
1 : 5-Diamino- ,, ...	Orange-red	0·18	320—322	0·53	300—310	320
2-Amino- ,, ...	Orange to red	2·36	296—300	1·80	306—308	304
1 : 8-Diamino- ,, ...	Orange to red	0·13		0·20	265—267	265
1 : 6-Diamino- ,, ...	Red	0·10	280—290	0·45	288—292	297
1 : 4-Diamino- ,, ...	Violet	—	(indef.)	0·05	~230	268
1 : 7-Diamino- ,, ...	Orange-yellow	0·20	300 (indef.)	0·15	286—289	292
2 : 7-Diamino- ,, ...	Yellow-orange	0·15	310—320	0·35	310—325	>330
Insoluble matter (discarded)	—	1·05	—	0·65	—	—
Aminohydroxy-anthraquinone, etc. + loss by difference	Deep purple lake	1·16	—	2·00	—	—
	Yields (%, wt.) on unrecovered anthraquinone :					
1-Amino-anthraquinone		22·9		25·1		
2- ,, ...		37·4		24·8		
Total diamines		12·0		23·8		

(*c*) *Without added catalyst.* When no metallic catalyst was used the product was resolved into unchanged anthraquinone (5·06 g.), 1-amino- (1·3 g.), 2-amino- (1·36 g.), and traces of 1 : 5-, 1 : 8-, and 2 : 7-diaminoanthraquinone.

(*d*) *With a vanadium catalyst in stronger acid.* An experiment was carried out in 98% sulphuric acid as described under (*b*). An exothermic reaction took place at 120° and the amination was allowed to proceed at 130° for 20 min. The composition of the product was very similar to that already described except that, in addition, a very small amount (<0·1 g.) of 2 : 6-diaminoanthraquinone (dibenzoyl derivative, m. p. 372—376°) was isolated from the sparingly soluble fraction.

Separation of Bands of Mixed Amines.—Pairs of amines which tended to run together were separately identified as follows :

2-Amino- and 1 : 8-diaminoanthraquinone. The former separated on recrystallisation from nitrobenzene, leaving the 1 : 8-diaminoanthraquinone in the mother-liquors. These were boiled with a little benzoyl chloride, and the yellow crystals of 1 : 8-dibenzamidoanthraquinone were filtered off and hydrolysed to the diamino-compound in 80% sulphuric acid at 100°.

1 : 4- *and* 1 : 6-*Diaminoanthraquinone.* The presence of the very small amount of 1 : 4-diaminoanthraquinone was revealed by the violet appearance of the leading edge of the band. It was readily removed from the recovered mixture by extraction with cold benzene.

1 : 7- *and* 2 : 7-*Diaminoanthraquinone.* These were separated by passing a solution in chlorobenzene containing 25% of pyridine through a small column of alumina. The less soluble fraction separating from the original chlorobenzene solution was conveniently chromatographed along with the mixture of 1 : 7- and 2 : 7-diamino-compounds recovered from the large column.

Amination of Aminoanthraquinones.—Vanadium pentoxide (0·075 g.) was added to 90% sulphuric acid (30 g.), followed by either 1- or 2-aminoanthraquinone (2·75 g.) and hydroxylamine sulphate (1 g.), and the mixture was heated to 160° in 45 min. and kept at that temperature for 4 hr. The yields were as follows: from 1-aminoanthraquinone, unchanged material (1·73 g.) and 1 : 5- (0·07 g.), 1 : 8- (0·12 g.), 1 : 6- (0·1 g.), 1 : 7- (0·15 g.), 1 : 4- (trace) diaminoanthraquinone; from 2-aminoanthraquinone: unchanged material (1·45 g.) and 1 : 6- (0·12 g.), 2 : 6- (0·08 g.), 2 : 7- (0·32 g.) diaminoanthraquinone.

Imperial Chemical Industries Limited, Dyestuffs Division,
Research Department, Blackley, Manchester, 9. [*Received, February* 13*th*, 1954.]

Physical Properties and Thermodynamic Functions of Trichloroacetonitrile.

By Mansel Davies and David G. Jenkin.

[Reprint Order No. 5128.]

The density, vapour pressure, refractive index, dielectric constant, and near infra-red and ultra-violet absorption spectra of liquid trichloroacetonitrile have been determined, and values of the thermodynamic functions calculated.

Trichloroacetonitrile is a lachrymatory liquid which has been used as a fumigant. A number of its simpler physical properties have been reported. Its solvent properties, in which capacity as a derivative of acetonitrile it might be expected to offer favourable characteristics, have not been reported. A prerequisite to its use as a solvent in physicochemical studies is adequate characterisation of its physical properties. The present account deals with the properties mentioned in the summary.

Experimental

Preparation and Purification.—The preparation from trichloroacetic acid was as follows:

$$Cl_3C{\cdot}CO_2H + EtOH = Cl_3C{\cdot}CO_2Et + H_2O$$
$$Cl_3C{\cdot}CO_2Et + NH_3 = Cl_3C{\cdot}CO{\cdot}NH_2 + EtOH$$
$$Cl_3C{\cdot}CO{\cdot}NH_2 = Cl_3C{\cdot}CN + H_2O$$

Ethyl trichloroacetate (200 g.) was fractionally distilled and treated with an equal volume of aqueous ammonia (*d* 0·880). Ammonia gas was bubbled through the flask for 0·5 hr. until reaction appeared to be complete. The mixture was kept cool overnight and the amide was filtered off and dried by suspending 100-g. portions in 600 ml. of carbon tetrachloride and removing the water by azeotropic distillation. The amide was filtered off and kept in a desiccator (KOH–paraffin wax).

Dehydration to trichloroacetonitrile was most efficiently done by heating the amide in 150-g. lots with its own weight of phosphoric oxide, the last 40 g. of which were shaken over the well-mixed constituents (McBee, Pierce, and Bolt, *Ind. Eng. Chem.*, 1947, **39**, 391. See also, *Ber.*, 1896, **29**, 2417; 1908, **41**, 2540; 1927, **60**, 1765; 1934, **67**, 1762): a further 20 g. were added before the nitrile was distilled off. The product was carefully refractionated from phosphoric oxide, the portion boiling at 85·8—86·0°/764 mm. being retained (yield 60% based on the amide).

Infra-red measurements showed that certainly less than 0·02% of the amide was present; a

similar figure represents the maximum amount of C–H-containing impurity (assumed to be acetonitrile). Neither N–H nor C–H absorptions could be detected in the liquid by use of a 1-mm. cell. After several months the liquid showed no signs of change even with traces of moisture, provided it was kept in complete darkness.

Another sample, kindly sent to us by the Deutsche Gold- und Silber-Scheideanstalt, had the same properties as our preparation.

Density.—Repeated determinations with a 10-ml. pyknometer having ground stoppers to prevent evaporation gave values (vacuum-corrected) :

$$\text{at } 25{\cdot}00^\circ \pm 0{\cdot}02^\circ : \quad d_4^{25} = 1{\cdot}4403 \pm 5 \times 10^{-4} \text{ g./c.c.}$$
$$\text{at } 35{\cdot}0^\circ \pm 0{\cdot}1^\circ : \quad d_4^{35} = 1{\cdot}4223 \pm 5 \times 10^{-4} \text{ g./c.c.}$$

The mean coefficient of cubical expansion over this range is $12{\cdot}_6 \times 10^{-4}$ per centigrade degree.

Vapour Pressure.—The semimicro-modification of the Smith–Menzies isoteniscope (Steinbach and Devor, *J. Chem. Educ.*, 1945, **22**, 496) has the advantages of requiring small amounts of liquid and of ensuring rapid thermal equilibrium with the bath. The bath was a 2-l. beaker containing water–glycerol which was vigorously stirred mechanically while being heated with a micro-burner. Its temperature was maintained constant within 0·1° for periods of 15 min. The scale of the wide-bore manometer, checked by a cathetometer, was read to 0·5 mm. Exposed-stem corrections were applied to the thermometer whose bulb was close to the vessel in which the liquid boiled : it was read to 0·05° and checked against N.P.L. standards. In four runs the extreme readings for the vapour pressure at 20·0° differed by 1·5 mm. Whilst the plots of $\log_{10} p$ against $1/T$ for each run suggested a slight curvature, the total number of acceptable points did not provide conclusive evidence of a deviation from a straight-line relation. In Table 1 a selection of the observed values are given with, for comparison, the percentage deviations from equation (1) and the Antoine equation, (2).

$$\log_{10} p \text{ (mm.)} = 7{\cdot}853 - 1783/T \ (T = {}^\circ\text{K}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$\log_{10} p \text{ (mm.)} = 7{\cdot}013 - 1275/(t + 222{\cdot}8) \ (t = {}^\circ\text{C}) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

TABLE 1. *Vapour pressures of trichloroacetonitrile.*

Temp.	p (mm.), obs.	Deviation (%) from (1)	Deviation (%) from (2)	Temp.	p (mm.), obs.	Deviation (%) from (1)	Deviation (%) from (2)
16·80°	49·0	−2·4	−0·4	50·15°	222·0	+2·3	+1·6
17·30	51·0	−1·0	+1·0	56·00	273·5	+0·7	−0·7
20·00	58·0	−1·2	+0·4	61·65	340·5	+1·2	+0·3
20·00	58·5	−0·4	+1·2	65·40	388·0	+0·6	0·0
23·40	68·5	−1·1	+0·4	66·90	458·5	+1·7	+1·3
26·55	80·0	0	+0·5	73·65	521·0	+1·4	+0·9
31·00	98·5	+0·8	+1·0	76·65	572·5	+0·6	+0·3
35·05	118·5	+1·5	+0·5	79·75	635·5	+0·7	+0·7
40·40	147·5	+0·9	0·0	83·40	709·5	+0·2	+0·5
47·00	192·5	+0·3	−0·5				

From these results the normal boiling point is 85·7° ± 0·2°/760 mm., the mean latent heat of evaporation is 8160 cal./mole, and the entropy of vaporisation at the boiling point (Trouton constant) is 22·8 cal./mole/°K. The corresponding figures for acetonitrile are 81·2°, 8030 cal./mole and 22·7 cal./mole/°K (Heim, *Bull. Soc. chim. Belg.*, 1933, **42**, 461). On the basis of the Trouton constants these liquids are unassociated.

Refractive Index.—A Pulfrich instrument was used with a sodium lamp and hydrogen discharge tube as sources : the temperature was maintained within ±0·1° by a water stream. The values were : $n_D^{20\cdot0} = 1{\cdot}4409 \pm 0{\cdot}0001$; $n_D^{27\cdot0} = 1{\cdot}4375 \pm 0{\cdot}0001$; $dn/dt = 4{\cdot}9 \times 10^{-4}$ per centigrade degree. The refractive index differences were : $n_D^{20} - n_C^{20} = (248 \pm 5) \times 10^{-5}$, $n_F^{20} - n_D^{20} = (620 \pm 5) \times 10^{-5}$, $n_G^{20} - n_D^{20} = (116 \pm 10) \times 10^{-5}$. The specific dispersion, $10^4(n_F - n_C)/[\text{Density}] = 59{\cdot}9$ ml./g. The addition of 0·2% of trichloroacetamide to the nitrile increased the refractive index by 0·0002. As the amide is produced from the liquid on exposure to light in the presence of moisture, this factor can be used to check the purity of the trichloroacetonitrile.

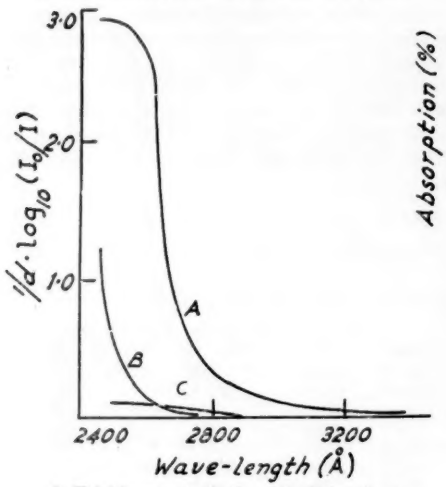
Ultra-violet Absorption.—The measurements made with a Hilger Uvi-spec spectrometer are shown in Fig. 1 together with the measurements, for comparison for the liquids chloroform and acetonitrile, relative to which (and to carbon tetrachloride) the absorption is shifted towards the visible.

Infra-red Absorption.—This was measured on a Grubb–Parsons S.3 single-beam instrument coupled to a Elliotronic 10-in. chart recorder. A rock-salt prism and cells of 1·0 mm., 0·1 mm., and capillary thickness were used.

The absorptions in the 3μ region were used to check the presence of $-NH_2$ and $-CH$ groups in the purified trichloroacetonitrile. Fig. 2 emphasises the satisfactory nature of the material. Later, a strong absorption was found near 1720 cm.$^{-1}$ in liquid which had been exposed to, *e.g.*, the total radiation from the Nernst filament source. This absorption is probably largely due to carbonyl impurities such as the amide or carbonyl chloride and, as the carbonyl group is one of the most intense absorbers in the infra-red, its presence provides a sensitive criterion of purity in trichloroacetonitrile.

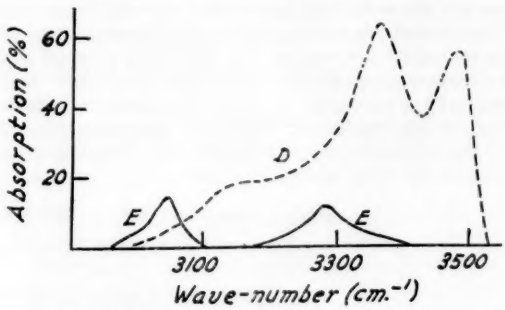
The trichloroacetonitrile molecule is assumed to have the same symmetry as methyl chloride, *i.e.*, C_{3v}. Accordingly its twelve fundamental vibrational modes consist of four symmetric ones (class A_1) and four doubly-degenerate (class E) vibrations, all of which should be Raman-active. Mecke (Landolt–Börnstein, " Tabellen," 6th edn., Vol. I, Part 2, Springer Verlag, Berlin, 1951) assigned the eleven Raman frequencies reported by Cheng (*Z. physikal. Chem.*, 1934, **26**, *B*, 288)

FIG. 1. *Absorptions in the near ultra-violet.*



A, Trichloroacetonitrile. *B*, Chloroform. *C*, Acetonitrile.

FIG. 2. *Infra-red absorptions* (1·0 *mm. cell*).



D, Trichloroacetamide (0·5% in trichloroacetonitrile).
E, Pure trichloroacetonitrile.

and if $r(CCl_3)$, the degenerate rocking frequency of the CCl_3-group is added at 350 cm.$^{-1}$ (which is suggested by combination bands in the infra-red), most of the observed frequencies can be accounted for. The symbols ν, b, s, and a refer to fundamental stretching, bending, symmetric, and antisymmetric modes respectively; the values are :

Class A_1 *vibrations*		*Class* E *vibrations*	
$\nu_s(CCl_3) = 487$ cm.$^{-1}$	$b_s(CCl_3) = 316$ cm.$^{-1}$	$b_a(CCl_3) = 265$ cm.$^{-1}$	$r(CCl_3) = 350$ cm.$^{-1}$
$\nu(CN) = 2250$ cm.$^{-1}$	$\nu(CC) = 1030$ cm.$^{-1}$	$\nu_a(CCl_3) = 792$ cm.$^{-1}$	$b(CCN) = 163$ cm.$^{-1}$

Table 2 shows the absorption centres measured and the intensities observed with the liquid in a 0·10-mm. cell: the absence of an entry in the 2nd and 5th columns means that the absorption was only observed in a longer (1·0 mm.) cell. Between 640 and 1400 cm.$^{-1}$, Cheng and Lecomte (*Ann. Physik*, 1936, **5**, 427) reported absorption maxima for trichloroacetonitrile in solution at 742, 790, 962, and 1010 cm.$^{-1}$. Clearly, in the pure liquid the weaker peak at 742 cm.$^{-1}$ is not resolved in the intense absorption from 750 to 814 cm.$^{-1}$.

This complete set of vibrational frequencies enables the thermodynamic factors for trichloroacetonitrile to be calculated by way of the standard partition functions. The values so obtained refer to an assumed ideal gas state at a pressure of one atmosphere and are based on the rigid-rotator, harmonic-oscillator model. The vibrational contributions were evaluated by using Torkington's tables (*J. Chem. Phys.*, 1950, **18**, 1373); for the other modes the relations given by

Wagman *et al.* (*J. Res. Nat. Bur. Stand.*, 1945, **34**, 143) were used. Assuming that the CCl_3-group had the same structure as in chloroform (Unterberger, Trambarulo, and Smith, *J. Chem. Phys.*, 1950, **18**, 565) and that the other bond lengths were: C–C, 1·48 Å, and C≡N, 1·16 Å (cf. Table 38, Stuart, "Die Struktur des Freien Moleküls," Springer Verlag, Berlin, 1952), then $I_1I_2I_3$, the product of the moments of inertia (Hirschfelder, *J. Chem. Phys.*, 1940, **8**, 431), = $1{\cdot}1632 \times 10^{-112}$ g.^{3} cm.^{6}; σ, the symmetry number, = 3, and M, the molecular weight, = 144·40.

TABLE 2. *Infra-red absorptions of trichloroacetonitrile.*

Absorption, cm.$^{-1}$	% absorption 0·1-mm. cell	Assignment	Absorption, cm.$^{-1}$	% absorption 0·1-mm. cell	Assignment
680	—	1026 − 350 = 674 *or* 350 × 2 = 700	1368	—	1026 + 350 = 1376
			1469	—	2250 − 792 = 1458
750 to 814	100	792	1580	30	792 × 2 = 1584
861	30	1026 − 163 = 863	1735	10	C = O of impurity
914	—	2250 − (1026 + 316) = 908	1816	10	1026 + 792 = 1818
			2090	—	2250 − 163 = 2087
968 to 980	100	487 × 2 = 974	2205	extremely weak	—
1025 to 1035	100	1030	2250	70	2250
1100	5	792 + 316 = 1108	2402	15	2250 + 163 = 2413
1133	—	792 + 350 = 1142	2502	—	2250 + 265 = 2515
1186	10	1026 + 163 = 1189	2728	—	2250 + 487 = 2737
1225	—	2250 − 1026 = 1224	3043	—	2250 + 792 = 3042
1274	20	792 + 487 = 1279	3278	—	2250 + 1026 = 3276

TABLE 3. *Thermodynamic functions calculated for trichloroacetonitrile in ideal gas state at 1 atmosphere* (cal./mole/°K).

T° K	273·15	298·15	300	400	600	800	1000
C°_p	22·22	22·95	23·00	25·17	27·59	28·90	29·70
$(H^\circ - H_0^\circ)/T$	15·16	15·79	15·83	17·92	20·79	22·67	24·00
$-(G^\circ - H_0^\circ)/T$	63·16	64·52	64·62	69·48	77·33	83·91	89·08
S°	78·32	80·31	80·45	87·40	98·12	106·58	113·08

Dielectric Constant.—The dielectric constant was measured for the liquid in a Hartshorn–Ward resonance circuit apparatus (*J. Inst. Elect. Eng.*, 1936, **79**, 597). The auxiliary cell, of rhodium-flashed stainless steel, in which the dielectric constant was measured, held approx. 10 ml. of liquid and had an air capacity of 80 $\mu\mu$F. Owing to the limits in the calibration of the variable condenser the capacity of the auxiliary cell had to be measured in series with a fixed silver–mica capacitor. This condition and the fact that the apparatus was originally designed to measure dielectric absorption markedly reduced the accuracy attainable in the measurement of the dielectric constant. From measurements at 210 kc./sec. a generous estimate of the uncertainty gave the value at 19°, $\varepsilon = 7{\cdot}85 \pm 0{\cdot}2$. When the Onsager relation (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) for the dipole moment (μ) in terms of dielectric constant (ε), refractive index (n), and density (d) of a pure polar liquid of molecular weight (M) is used, *i.e.*,

$$\mu^2 = \frac{9MkT(\varepsilon - n^2)(2\varepsilon + n^2)}{4\pi N \cdot d\varepsilon(n^2 + 2)^2}$$

the value $\mu = 1{\cdot}93$ D is evaluated. On the simplest assumptions for constancy of group moments, this value should be equal to the difference between the moments for acetonitrile and chloroform, which is 2·1 D. The agreement is not unreasonable.

We thank the University of Wales for a Research Studentship to one of us (D. G. J.) during the 1953—54 session: the Deutsche Gold- und Silber-Scheideanstalt of Frankfurt-am-Main are thanked for a sample of trichloroacetonitrile, the Royal Society Grants Committee for the dielectric loss apparatus, and Imperial Chemical Industries Limited for the provision of the Uvispek Spectrometer.

THE EDWARD DAVIES CHEMICAL LABORATORIES,
THE UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH. [*Received, February 16th*, 1954.]

Colouring Matters of the Aphididæ. Part XI. Pigments from* Hamamelistes *Species.*

By S. F. MacDonald.

[Reprint Order No. 4118.]

The pigments of *Hamamelistes spinosus*, Shimer, and *H. betulae*, Mordvilko, represent a new type of aphin series. The native pigments (heteroaphins) of these aphids are converted enzymically into the same rhodoaphin, $C_{30}H_{22}O_{11}$.

The rhodoaphin has been reduced to a typical erythroaphin, and comparison of the rhodoaphin with hydroxy- and dihydroxy-erythroaphin-*fb* suggests that it is a dihydroxyerythroaphin containing a further oxygen atom of unknown function.

Aphins so far described (Duewell, Human, Johnson, MacDonald, and Todd, *J.*, 1950, 3304) have belonged to aphin series of the type first described by Sorby [*Quart. J. Microscop. Sci.*, 1871, II (N.S.), 352]. The native pigments, protoaphins, were converted enzymically into xanthoaphins and thence by chemical methods successively into chrysoaphins and erythroaphins. Though minute amounts of the four pigments were readily detected and distinguished, the corresponding pigments (*e.g.*, erythroaphins) from different species could be clearly distinguished only by *X*-ray powder photographs and infra-red spectra.

The only other aphid pigments found which were apparently related to these aphins were those of *Hamamelistes* species, which resembled the erythroaphins in colour and spectra but lacked the usual precursors. Work was begun with the North American *Hamamelistes spinosus*, Shimer, and continued first with the British *H. betulae*, Mordvilko, then with *H. spinosus* again. Both are primitive aphids found, surrounded by masses of wax and sugar, in shallow galls opening on the under side of leaves of the white birch. They are unusual among aphids in that their wings are horizontal when at rest. The methods of Duewell *et al.* (*loc. cit.*) for the preliminary examination had to be modified to give adequate separation of the pigments by partition. The only native pigment detected was the heteroaphin, a water-soluble red pigment occurring in the hæmolymph in amounts representing about 1% of the live-insect weight. It is unstable in extracts unless enzymes have been inactivated by heat or organic solvents. In unstabilized extracts, and in stabilized extracts to which the freshly pulped insects have been added, heteroaphin is rapidly converted into rhodoaphin, a second red pigment which is soluble in ether. These names imply a relation to the previously known aphin series which is justified by the work described below. In accordance with the convention (Duewell, Human, Johnson, MacDonald, and Todd, *Nature*, 1948, **162**, 759), suffixes are added to indicate the insect source: *sp* from *H. spinosus* and *be* from *H. betulae*.

Except in their solubility, the heteroaphins-*sp* and -*be* resemble erythroaphin rather than any of its precursors, becoming green reversibly with alkali and showing visible absorption (Table 1). Although their enzymic conversion into rhodoaphins parallels that of protoaphin-*ph* into xanthoaphin-*ph*, *H. betulae* pulp does not bring about the latter change. Also, these heteroaphins are converted into rhodoaphins by mild acid, but the conversion of protoaphins into xanthoaphins can only be carried out enzymically and appears to be complex (*J.*, 1952, 4925). Although there are no apparent differences between the heteroaphins-*sp* and -*be*, it is uncertain whether or not they are identical for they have not been obtained crystalline.

Solutions of the rhodoaphins, obtained when *H. spinosus* or *H. betulae* were crushed a few minutes before extraction, were strikingly similar to those of the erythroaphins in colour and spectra (Table 1); they also became green in alkali but differed in being unstable in concentrated sulphuric acid. However, methods applicable to the erythroaphins

* Part X, *J.*, 1954, 1285.

resulted in a poor yield of crystalline rhodoaphin-*sp* and failed to give crystalline rhodoaphin-*be*.

Unsuccessful attempts were made to show that the rhodoaphins were oxoerythroaphins by making and comparing the oximes. In these experiments with erythroaphin-*fb*, spectra resembling that of the rhodoaphins were noted when hot solutions of the erythroaphin were treated with ammonia and air, and the product was isolated as diaminoerythroaphin-*fb* (Part VII, Brown, Johnson, MacDonald, Quayle, and Todd, *J.*, 1952, 4928). Though this product did not resemble the rhodoaphins in basicity and stability, it was readily converted into dihydroxyerythroaphin-*fb* which did. A hydroxyerythroaphin-*fb* was also obtained for comparison, though no trihydroxyerythroaphin could be prepared (Part VII, *loc. cit.*). Comparison of the spectra of these pigments (Table 1) suggested that the rhodoaphins might be trihydroxyerythroaphins. In alkali, 60% perchloric acid, under reducing conditions (acid or alkaline), and after conversion of the pigments into metal complexes (particularly those with nickel), the spectra showed the same regularity but none were so characteristic as those in chloroform.

TABLE 1. *Absorption maxima* (mμ).

Erythroaphin-*fb*	(in $CHCl_3$) 589, 563, 521, 485, 447, 421
Hydroxyerythroaphin-*fb*	(in $CHCl_3$) 592, 563, 523, 488, 450, 425
Dihydroxyerythroaphin-*fb*	(in $CHCl_3$) 595, 567, 526, 490, 453, 426
Rhodoaphin-*sp* and -*be*	(in $CHCl_3$) 596, 568, 528, 454, 427—429
Heteroaphin-*sp* and -*be*	(in MeOH) 551, 515, 443

The rhodoaphins were then found to decompose, like dihydroxyerythroaphin-*fb* (Part VII, *loc. cit.*), when their solutions in chloroform or ether were shaken with water, with buffers of pH 5—8, or with aqueous sodium hydrogen carbonate, the red-brown product separating at the interface. Stronger alkali extracts the rhodoaphins as their green salts, and the pigments are returned unchanged to the organic layer after acidification. Satisfactory yields of the crystalline rhodoaphins-*be* and -*sp* were then obtained by maintaining acid conditions during their extraction. Their identity was established by *X*-ray powder photographs and infra-red spectra. Analysis of rhodoaphin-*be* indicated a formula $C_{30}H_{22}O_{11}$ which is that of a trihydroxyerythroaphin. These rhodoaphins show hydroxyl absorption in their infra-red spectra as do hydroxy- and dihydroxy-erythroaphin-*fb*; the erythroaphins do not.

The pigments also show gradations in stability and partition behaviour (Table 2), in acidity, and in the speed with which they give Blount's colour reaction with acetic anhydride and mineral acid. Unlike the spectra, none of these methods will distinguish the rhodoaphins from dihydroxyerythroaphin-*fb*. As their partition behaviour is not that expected in a trihydroxyerythroaphin, the rhodoaphins are regarded as a dihydroxy-erythroaphin having a further oxygen atom with some other function.

TABLE 2.

	Stability			Partition		
	In conc. H_2SO_4	In pyridine at 100°	In $CHCl_3$ with aq. $NaHCO_3$	% H_2SO_4 extracting pigment from $CHCl_3$	% Aq. resorcinol extracting pigment from $CHCl_3$	Partition between CS_2 and MeOH: % in MeOH
Erythroaphin-*fb*	Stable	Rapid decomp.	Stable	72	>66	<3
Hydroxyerythroaphin-*fb*	Slow decomp.	Slow decomp.	Stable	*ca.* 68	*ca.* 50	*ca.* 20
Dihydroxyerythroaphin-*fb* and Rhodoaphin-*sp* and -*be*	Rapid decomp.	Stable	Decomp.	<72	33	*ca.* 85

The removal of hydroxyl groups from anthraquinones (Dimroth and Fick, *Annalen*, 1916, **411**, 315) suggested reduction of the rhodoaphins to an erythroaphin. After model experiments with hydroxy-, diamino- and dihydroxy-erythroaphin-*fb* (Part VII, *loc. cit.*), the rhodoaphins were reduced to typical erythroaphins as judged by their spectra,

stability, amination, and partition behaviour. These were not obtained in an obviously crystalline condition, and the 6—10 μ regions in their spectra suggested that they might be impure erythroaphin-*fb*.

Experimental

Spectra were measured in chloroform which had been washed several times with concentrated sulphuric acid, kept for some hours over potassium hydroxide, distilled, and stabilized by the addition of pure dry ether (5% v/v). When pure but unstabilized chloroform was used, the optical densities in the ultra-violet region increased rapidly during measurement, apparently because of the formation of hydrogen chloride. When Beckman or Unicam instruments were used, the two small peaks at *ca.* 490 and *ca.* 595 mμ were not always detected in solutions of dihydroxyerythroaphin-*fb* and the rhodoaphins. These at *ca.* 595 mμ were measured visually when necessary; their sharpness makes them the most convenient guide in work with these pigments.

Preliminary Examination of the Insects.—The water and methanol used contained tartaric acid (0·5%). About 15 live insects were ground with methanol (2 drops); when water (1·5 c.c.) and ether (1·5 c.c.) were added to the mixture the red heteroaphin remained in the aqueous phase, and the nearly colourless ether layer contained only traces of pigment. The live insects were ground with water (1 drop) and, after being kept for 1 min. for fermentation, stirred with methanol (2 drops); after addition of ether and water as before, the aqueous phase was nearly colourless and contained only traces of pigment, the red rhodoaphin being in the ether.

Non-enzymic Conversion of Heteroaphin.—Live *H. betulae* were ground with methanol, and 10% hydrochloric acid (1·5 c.c.) was added. After a few minutes, ether and water were added; only traces of pigment were found in the aqueous layer, but rhodoaphin-*be* was identified in the ether by its colour and spectrum.

Rhodoaphin-sp *from* H. spinosus.—(i) The insects (5 g.; preserved for 6 weeks at 0°) were freed from wax and sugar by, successively, acetone, ether, benzene, and acetone. The pigment was extracted by grinding and filtering with, successively, acetone, water, and 80% acetone. The last extract, containing the bulk of the pigment, was evaporated *in vacuo* and the residue extracted with ether. After being washed with water, the ethereal layer was evaporated and the residue crystallized from hot ethanol. Rhodoaphin-*sp* formed small rods (*ca.* 2 mg.).

(ii) By the method given for rhodoaphin-*be*, the insects (6 g.) gave rhodoaphin-*sp* (25 mg. crude, 4·8 mg. crystalline) (Found: N, 0·0%). The infra-red spectrum of a mull in Nujol showed maxima at 632, 720, 838, 854, 881, 943, 975, 1048, 1076, 1115, 1155, 1175, 1203, 1230, 1255, 1292, 1304, 1571, 1633, 2720, 3270 cm.$^{-1}$; in the hydroxyl region there was also a shoulder at 3170 cm.$^{-1}$.

Rhodoaphin-be *from* H. betulae.—The live insects (3·8 g.) were repeatedly washed with light petroleum (b. p. 40—60°) by decantation to remove excess of wax, ground with aqueous tartaric acid (0·5%), allowed to ferment for a few minutes, and extracted with aqueous methanol (85%, acidified with tartaric acid; 3 × 30 c.c.). The methanol was washed with light petroleum (b. p. 40—60°), water was added, and the pigment extracted from the aqueous methanol with ether (total, 60 c.c.). The ether was diluted with light petroleum (b. p. 40—60°; 2 vols.), filtered, and concentrated under slightly reduced pressure. The granular crude product (20 mg.) which separated was extracted with ether (10 c.c.; thimble), ethanol (1 c.c.) was added, and the extract concentrated and kept for 5 days at 0°. *Rhodoaphin*-be separated as fine red needles (7·2 mg.) and the mother liquors gave more (1·6 mg.) of the well-crystallised material (Found: C, 64·5; H, 4·3. $C_{30}H_{22}O_{11}$ requires C, 64·5; H, 4·0%).

Erythroaphin.—(i) *From rhodoaphin*-be. Amorphous rhodoaphin-*be* from the mother-liquors from the crystalline product above, and crude granular rhodoaphin-*be* (7·8 mg.) prepared as above from *H. betulae* (1·1 g.) were available. Both specimens had maxima at 596 μ and were destroyed by the treatment with bicarbonate, so related pigments were absent.

The combined specimens were reduced and the product purified exactly as in the analogous reduction of dihydroxyerythroaphin-*fb* (*J.*, 1952, 4932). The erythroaphin (3 mg.) separated from chloroform–ethanol in granular form. Absorption maxima in $CHCl_3$: 588—589, 563, 521, 447, 423—424, 335, 318, 255 mμ; min. at 581, 536, 499, 431, 361, 328, 314 mμ.

(ii) *From rhodoaphin*-sp. Amorphous rhodoaphin-*sp* (20 mg.) from the mother-liquors from the crystalline product was reduced and the product purified as in (i) except that the chloroform solution of the erythroaphin was also washed with 50% aqueous resorcinol. The product was granular. Absorption max. in $CHCl_3$: 588, 563, 521, 486, 448, 422 mμ.

Its identity was confirmed by 1 hour's heating at 90° in aqueous dioxan containing nitrobenzene and ammonium carbonate, giving a diaminoerythroaphin (*J.*, 1952, 4928), identified in the comparison spectroscope and by extraction from chloroform into 10% hydrochloric acid.

The author is grateful to Dr. W. Cochran for the *X*-ray powder photographs, to Dr. R. N. Haszeldine and Dr. R. N. Jones for visible and infra-red spectra, and to Mr. H. L. G. Stroyan who identified the insects. Grateful acknowledgment is made to the Wellcome Trustees for a Fellowship, during the tenure of which part of this work was carried out.

University Chemical Laboratory, Cambridge.
Department of Medical Research, University of Toronto. [*Received February 21st*, 1953.]

Studies on Phosphorylation. Part XII. Selective Anionic Dealkylation of Neutral Esters of Phosphoric and Thiophosphoric Acids.*

By J. Lecocq and A. R. Todd.

[Reprint Order No. 5198.]

The method of anionic fission developed for monodebenzylation of neutral esters of the oxyacids of phosphorus (Part VII, *J.*, 1950, 2031) can be extended to the removal of alkyl groups. Selective monodealkylation of a number of esters of phosphoric and thiophosphoric acids is described, and the conditions governing its success are discussed.

In Part VII of this series (Clark and Todd, *J.*, 1950, 2031) it was shown that neutral esters of phosphorous and phosphoric acid containing one or more benzyl groups can be monodebenzylated by heating them with inorganic salts such as lithium chloride in ethoxyethanol solution. The mechanism postulated for this anionic fission involved an attack by the anion of the salt on the electrophilic CH_2 group in the benzyl residue :

$$Cl^- \rightarrow Ph\cdot CH_2\cdot O\cdot PO(OR)_2 \longrightarrow Ph\cdot CH_2Cl + {}^-O\cdot PO(OR)_2$$

As was to be expected on the basis of this mechanism lithium chloride had no effect on triphenyl phosphate, but the fact that it brought about monodebenzylation of dibenzyl phosphoramidate (aminophosphonate) led to the suggestion (*loc. cit.*) that the method might, under appropriate conditions, be applicable to groups, such as alkyl, with considerably less electrophilic character than the benzyl group. The present paper records a number of experiments which indicate that this is indeed so.

For the investigation, a number of hitherto undescribed mixed triesters of phosphoric acid containing both aryl and alkyl groups were prepared, as well as some neutral thiol- and thiono-phosphates. Mixed esters containing phenyl as well as alkyl groups seemed of particular interest since it was expected that the phenyl groups would indirectly increase the electrophilic character of the α-carbon of the alkyl groups and so facilitate monodealkyl-

Monodealkylation of phosphates and thiophosphates with lithium chloride at 100°.

Ester	Yield (%) of monodealkylated product	Ester	Yield (%) of monodealkylated product
Diphenyl *n*-propyl phosphate ...	85	Diphenyl *n*-propyl thionophosphate	27
Phenyl di-*n*-propyl phosphate ...	50	Diethyl *S*-phenyl thiophosphate	75
Tri-*n*-propyl phosphate	25	*S*-Ethyl diphenyl thiophosphate	No reaction
Diphenyl *iso*propyl phosphate ...	85		
*cyclo*Hexyl diphenyl phosphate	45		

ation by the above mechanism. Each ester was treated with lithium chloride under standard conditions, *viz.*, in 2-ethoxyethanol solution at 100° for 3 hours. The results obtained are summarised in the Table.

* Part XI, *J.*, 1953, 2257.

In considering these results it should be remembered that the yields quoted are based on the weight of isolated diester (either as such or as an appropriate derivative) and are thus only very roughly quantitative; again, it cannot be assumed that the chosen reaction conditions are optimum in any case. Pyrolytic decomposition of phosphates at high temperatures causes dealkylation: for example, diphenyl *iso*propyl phosphate is converted almost quantitatively into diphenyl hydrogen phosphate at *ca.* 180°. This type of decomposition is certainly not the main cause of the dealkylation observed in our studies; at 100°, in the absence of lithium chloride, diphenyl *n*-propyl phosphate was unaffected and only minor decomposition occurred with diphenyl *iso*propyl phosphate (≯16%), *cyclo*hexyl diphenyl phosphate (≯12%), and diethyl *S*-phenyl thiophosphate (≯10%).

From the Table it can be seen that, as expected, dealkylation is made easier by the presence of phenyl groups. It also appears that steric factors are important; it is hard to account otherwise for the comparatively low yield from *cyclo*hexyl diphenyl phosphate. Variation in yields when different salts are used has been reported for the monodebenzylation of neutral phosphates (Clark and Todd, *loc. cit.*); similar variations are observed in the removal of alkyl groups. Salts are more powerful debenzylating agents than tertiary bases. Thus, dibenzyl phosphoramidate resists the action of 4-methylmorpholine but is monodebenzylated by lithium chloride (Clark and Todd, *loc. cit.*); in the same way, diphenyl *n*-propyl phosphate is unaffected by refluxing 4-methylmorpholine (b. p. 115°) for 3 hr., although under the same conditions conversion of tribenzyl phosphate into dibenzyl phosphate is well-nigh quantitative. The addition of a small amount (5%) of water to the ethoxyethanol used in the dealkylation experiments caused little diminution in the yield of dealkylated product in the case of diphenyl *n*-propyl phosphate. Large amounts of water are, however, deleterious; thus, when the same ester is refluxed with calcium chloride in 98% ethanol, the yield of calcium diphenyl phosphate was 22%, and in 60% ethanol it fell to 3%.

It is known that many thiophosphates form complexes with silver nitrate, the metal presumably becoming co-ordinated to a sulphur atom; the sulphonium salt so formed can then break up under appropriate conditions of temperature with expulsion of an alkyl group (cf., for example, Emmett and Jones, *J.*, 1911, **715**; Pistschimuka, *J. pr. Chem.*, 1911, **84**, 746). However, diphenyl *n*-propyl thionophosphonate gave only a trace of precipitate with silver nitrate, whereas *S*-ethyl diphenyl thiophosphate gave a copious precipitate of complex salt. Since the former ester is dealkylated under our standard conditions whereas the latter is not, it seems clear that lithium chloride dealkylation of thiophosphates is essentially analogous to that of the phosphates and differs from the silver nitrate reactions mentioned above. The failure of the attempted dealkylation of *S*-ethyl diphenyl thiophosphate with lithium chloride under the standard conditions is probably explained by the smaller electronegativity of sulphur compared with oxygen.

Pistschimuka (*J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1406) reported the isolation of two distinct sodium salts of diphenyl hydrogen thiophosphate; an insoluble salt $(PhO)_2PO{\cdot}SNa$ he claimed to obtain by the action of sodium methoxide on triphenyl thionophosphate, and a soluble one $(PhO)_2PS{\cdot}ONa$ by treating diphenyl thionophosphorochloridate with sodium hydroxide. We have been unable to confirm these findings. Treatment of triphenyl thionophosphate with sodium methoxide or sodium hydroxide gave the same soluble sodium salt as lithium chloride dealkylation of diphenyl *n*-propyl thionophosphate. Our findings thus parallel those of Mastin, Norman, and Weilmuenster (*J. Amer. Chem. Soc.*, 1945, **67**, 1662) and of Foss (*Acta Chem. Scand.*, 1947, **1**, 8) on salts of dialkyl hydrogen thiophosphates, and it seems clear that the claim to separate existence of isomeric thiol- and thiono-acid salts cannot be upheld.

Because of its potential application in the nucleotide field, we are interested in the possibility of direct replacement of alkyl groups in neutral phosphates by hydrogen using anionic fission. This we were unable to effect using calcium hydride, while lithium aluminium hydride reacted vigorously with triphenyl phosphate yielding phosphine and phenol and a similar reaction occurred with diphenyl *n*-propyl and phenyl di-*n*-propyl phosphate. Karrer and Jucker (*Helv. Chim. Acta*, 1952, **35**, 1586) have independently observed a similar action of lithium aluminium hydride on cetyl dihydrogen phosphate. This reaction of

lithium aluminium hydride is analogous to that of phenylmagnesium bromide which displaces the alkoxy-groups in alkyl phosphates (Gilman and Robinson, *Rec. Trav. chim.*, 1929, **48**, 328).

Experimental

Diphenyl n-*Propyl Phosphate*.—Diphenyl phosphorochloridate (26·8 g.; Brigl and Müller, *Ber.*, 1939, **72**, 2121) in dry benzene (25 c.c.) was added slowly to an ice-cold stirred solution of *n*-propanol (6 g.) and dry pyridine (7·9 g.) in benzene (50 c.c.). The temperature rose slightly and pyridine hydrochloride began to separate during the addition. The mixture was set aside overnight, water was added, and the benzene layer separated, washed with aqueous sodium carbonate, then with water, and finally dried (Na_2SO_4). After evaporation, the residue (28 g.) was distilled under reduced pressure, care being taken to avoid overheating (which causes decomposition). *Diphenyl* n-*propyl phosphate* distilled as a colourless liquid at 148—150°/0·1 mm. and had $n^{15·5}$ 1·5242 (Found: C, 61·9; H, 6·2. $C_{15}H_{17}O_4P$ requires C, 61·6; H, 5·9%).

Diphenyl iso*Propyl Phosphate*.—Prepared as above from diphenyl phosphorochloridate (26·8 g.) and *iso*propanol (6 g.), the crude ester weighed 28 g. When distillation of the ester was attempted under a pressure of 0·1 mm. brisk decomposition began when the bath temp. reached 180°; after 15 min. at a bath temp. of 225° the material was completely converted into diphenyl hydrogen phosphate, m. p. and mixed m. p. 68—70°. *Diphenyl* iso*propyl phosphate* was therefore purified by short-path distillation at 98—100°/10^{-4} mm., forming a colourless liquid, $n^{15·5}$ 1·5232 (Found: C, 61·1; H, 5·6. $C_{15}H_{17}O_4P$ requires C, 61·6; H, 5·9%).

cyclo*Hexyl Diphenyl Phosphate*.—Prepared as above, the crude ester (30·5 g. from 26·8 g. of diphenyl phosphorochloridate) crystallised slowly when kept at 0°. Recrystallised from light petroleum (b. p. 40—60°), it had m. p. 34—35° (Found: C, 65·2; H, 6·2. Calc. for $C_{18}H_{21}O_4P$: C, 65·1; H, 6·3%).

Phenyl Di-n-*propyl Phosphate*.—Phenyl phosphorodichloridate (21·1 g.; Brigl and Müller, *loc. cit.*) in dry benzene (25 c.c.) was added slowly with stirring to an ice-cold solution of *n*-propanol (12 g.) and dry pyridine (15·8 g.) in benzene (100 c.c.). The mixture was set aside overnight, then worked up as described for diphenyl *n*-propyl phosphate. The *product* distilled at 165° (bath-temp.)/0·1 mm. (Found: C, 56·5; H, 7·3. $C_{12}H_{19}O_4P$ requires C, 55·8; H, 7·4%).

Diphenyl Thionophosphorochloridate.—The following modification of the method of Autenrieth and Meyer (*Ber.*, 1925, **58**, 840) is recommended. Phenol (94 g.) in dry benzene was slowly added to a suspension of powdered sodium (23 g.) in benzene (*ca.* 500 c.c.). Then the mixture was stirred at room temperature until the reaction slackened, and reaction was completed by 5 hours' refluxing. The suspension of sodium phenoxide so obtained was cooled to −5° and a solution of thiophosphoryl chloride (84 g.) in dry benzene (100 c.c.) added slowly with stirring. When all had been added the mixture was allowed to come to room temperature and was then heated under reflux for 2 hr., cooled, and filtered. The filtrate was washed with water, dried (Na_2SO_4), and evaporated. The residual oil (126 g.) solidified; recrystallised from 98% ethanol or light petroleum, it had m. p. 67—68°.

Diphenyl n-*Propyl Thionophosphate*.—Diphenyl thionophosphorochloridate (33·2 g.) was added to a stirred solution of *n*-propanol (14 g.) and dry pyridine (9·2 g.) in benzene (100 c.c.). Precipitation of pyridine hydrochloride was very slow and the mixture was set aside for 2 weeks to ensure complete reaction. Water was then added and the benzene layer was washed successively with cold dilute hydrochloric acid, aqueous sodium carbonate, and water, before being dried (Na_2SO_4) and evaporated. The residue was distilled in a short-path still at 106°/2·17 × 10^{-3} mm., giving *diphenyl* n-*propyl thionophosphate* (25·3 g.) as a colourless liquid, n^{16} 1·5578 (Found: C, 58·0; H, 5·4. $C_{15}H_{17}O_3SP$ requires C, 58·4; H, 5·5%). The ester was also prepared in rather similar yield by treating diphenyl thionophosphorochloridate with sodium *n*-propoxide (1 mol.) in dry ether or benzene; reaction in this case was complete after 24 hr. at room temperature.

Diethyl S-*Phenyl Thiophosphate*.—Thiophenol (21·5 g.) was added to powdered sodium (4·5 g.), suspended in benzene, and the reaction completed by 3 hours' heating under reflux. The suspension was then cooled and diethyl phosphorochloridate (33·7 g.; McCombie, Saunders, and Stacey, *J.*, 1945, 380) dissolved in benzene (50 c.c.) was added slowly with stirring. The mixture was set aside overnight, then filtered, and the filtrate was washed first with aqueous sodium hydroxide, then with water, dried (Na_2SO_4), and evaporated. The residual *diethyl* S-*phenyl thiophosphate* (43 g.) distilled at 108°/0·2 mm. as a colourless liquid, n^{16} 1·5240 (Found: C, 49·1; H, 6·1. $C_{10}H_{15}O_3SP$ requires C, 48·9; H, 6·1%).

S-*Ethyl Diphenyl Thiophosphate.*—Ethanethiol (36·9 g.) was added in one portion to a suspension of pulverised sodium (13·5 g.) in benzene, and the mixture stirred at room temperature till the main reaction was over. The suspension was heated to 70° for 1 hr. to complete reaction, then cooled to 0°, and diphenyl phosphorochloridate (143 g.) dissolved in dry benzene (200 c.c.) was added slowly with stirring. The mixture was stirred at room temperature for a further 3 hr., then filtered. The filtrate was thoroughly washed with aqueous ammonia (10%), hydrochloric acid, and water, then dried (Na_2SO_4) and evaporated. The residue distilled at 140°/0·02 mm., giving the colourless liquid *ester* (111 g.) (Found: C, 56·9; H, 4·8. $C_{14}H_{15}O_3SP$ requires C, 57·1; H, 5·1%).

Monodealkylation of Triesters of Phosphoric and Thiophosphoric Acids with Lithium Chloride. Standard Procedure.—The neutral ester (0·01 mole) was heated for 3 hr. at 100° with anhydrous lithium chloride (3 equivs.) in 2-ethoxyethanol (25 c.c.). Ethoxyethanol was removed under reduced pressure at <100° and water was added to the cooled product. Unchanged triester was extracted with ether (2 × 20 c.c.). The aqueous layer was acidified with dilute sulphuric acid and then extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated and the acidic ester identified as such or as an appropriate derivative. The following products were obtained from the several esters examined: Diphenyl hydrogen phosphate, identified as such (m. p. 68—70°) or as its cyclo*hexylammonium* salt which crystallised from ethanol as silky needles, m. p. 200—201° (Found: C, 62·2; H, 6·7; N, 4·2. $C_{18}H_{24}O_4NP$ requires C, 61·9; H, 6·9; N, 4·0%). In a dealkylation experiment with diphenyl *n*-propyl phosphate and calcium chloride, *calcium diphenyl phosphate* was obtained; it formed bunches of short colourless needles when recrystallised from ethanol [Found: C, 53·5; H, 3·8. $(C_{12}H_{10}O_4P)_2Ca$ requires C, 53·5; H, 3·7%].

Phenyl *n*-propyl hydrogen phosphate gave a cyclo*hexylammonium* salt, colourless needles (from ethanol), m. p. 124—125° (Found: C, 57·1; H, 8·3. $C_{15}H_{26}O_4NP$ requires C, 57·5; H, 8·6%). This acid ester was also obtained by alkaline hydrolysis of diphenyl *n*-propyl phosphate.

On dealkylation with lithium chloride, tri-*n*-propyl phosphate (Dutton and Noller, *J. Amer. Chem. Soc.*, 1953, **55**, 424) gave di-*n*-propyl hydrogen phosphate, identified as its lead salt, m. p. 149—151° (Cavalier and Prost, *Bull. Soc. chim.*, 1900, **23**, 678).

Diphenyl hydrogen thiophosphate, obtained as an oil by the action of lithium chloride on diphenyl *n*-propyl thionophosphate, was treated with *cyclo*hexylamine in ether. The cyclo*hexylammonium* salt recrystallised from water as colourless needles, m. p. 127—128°, containing both S and P (Found: C, 59·4; H, 6·7. $C_{18}H_{24}O_3NSP$ requires C, 59·2; H, 6·6%). The same salt (m. p. and mixed m. p. 127—128°) was obtained by hydrolysis of diphenyl thionophosphorochloridate with potassium hydroxide and treatment of the acid obtained with *cyclo*hexylamine.

Ethyl *S*-phenyl hydrogen thiophosphate, obtained from diethyl *S*-phenyl thiophosphate as an oil, yielded a cyclo*hexylammonium* salt crystallising from acetone as colourless needles, m. p. 128—129°; the salt contained both S and P (Found: C, 52·7; H, 7·2; N, 4·9. $C_{14}H_{24}O_3NSP$ requires C, 53·0; H, 7·6; N, 4·4%).

Our thanks are due to the Centre National de la Recherche Scientifique and the Medical Research Council for a scholarship held by one of us (J. L.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 11th*, 1954.]

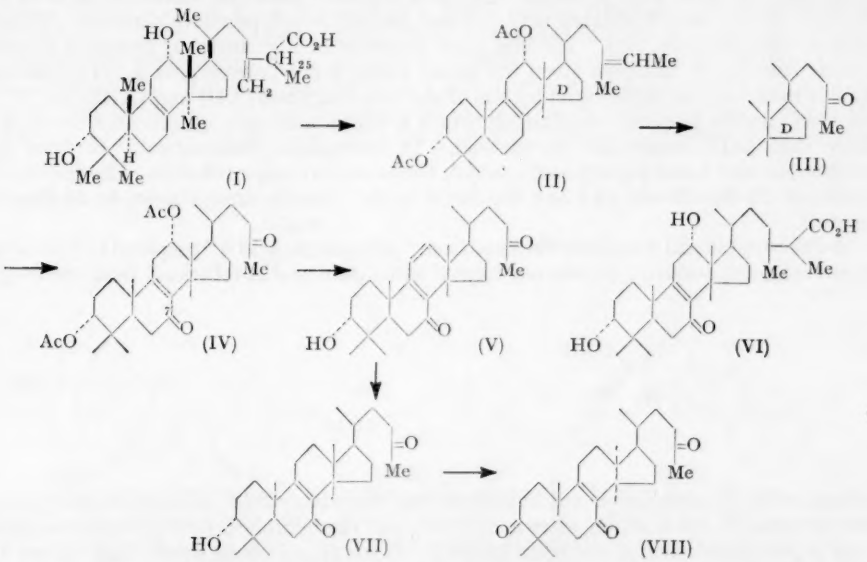
The Chemistry of the Triterpenes and Related Compounds. Part XXIV. The Conversion of Polyporenic Acid A into a Lanosterol Derivative.*

By T. G. Halsall and R. Hodges.

[Reprint Order No. 5148.]

Following extensive degradative investigations a structure for polyporenic acid A, $C_{31}H_{50}O_4$, was proposed (Halsall, Hodges, and Jones, *J.*, 1953, 3019). The proof of the structure has now been completed by the conversion of the acid and of lanosterol into a common C_{28} degradation product.

Structure (I) for polyporenic acid A was suggested by Halsall, Hodges, and Jones (*J.*, 1953, 3019) on the basis of degradative evidence and a probable biogenetic relationship with eburicoic acid and polyporenic acid C. Final proof of the correctness of (I) has now been obtained by the conversion of polyporenic acid A into a compound of known structure derived from lanosterol. Roth, Saucy, Anliker, Jeger, and Heusser (*Helv. Chim. Acta*, 1953, **36**, 1908) have also recently carried out the conversion of polyporenic acid A and lanosterol into a common, but different, degradation product.



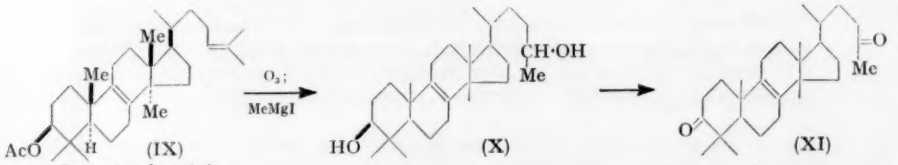
Ozonolysis of the diacetate of decarboxylated polyporenic acid A (II) has already been shown to give a methyl ketone (III) (Halsall *et al.*, *loc. cit.*). Oxidation of this ketone with chromic acid for a short time introduced a second oxo-group at $C_{(7)}$ giving (IV). (Oxidation for a longer time gave the 7 : 11-diketone.) Treatment of (IV) with methanolic potassium hydroxide gave the dienone (V). This reaction is analogous to that with (VI), already described by Halsall, Jones, and Lemin (*J.*, 1953, 468), in which the corresponding dienone is formed. Reduction of (V) with zinc dust in acetic acid gave the αβ-unsaturated ketone (VII) which was oxidised to the triketone (VIII).

" Isocholesteryl acetate " which contains lanostadienyl acetate (IX) was ozonised, the crude product was treated directly with methylmagnesium iodide and the resulting diol (X) was oxidised with chromic acid in acetone to the corresponding diketone (XI). After purification and characterisation (XI) was oxidised with chromic acid in acetic acid giving

* Part XXIII, *J.*, 1954, 1905.

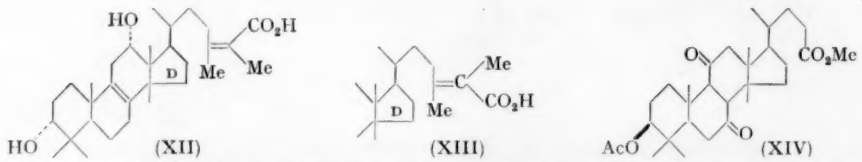
the triketone (VIII), identical (mixed m. p.; infra-red spectra in carbon tetrachloride) with that prepared from polyporenic acid A.

These results finally prove the correctness of structure (I) for polyporenic acid A, which is therefore 3α : 12α-dihydroxyeburico-8 : 24(28)-dien-26-oic acid. The only feature of the structure which remains to be elucidated is the stereochemistry of $C_{(25)}$.



In the preparation of decarboxylated polyporenic acid A, it was found that, when the crude acid obtained by the hydrolysis of methyl polyporenate A was decarboxylated, some ether-insoluble acid (20%) was obtained, besides the expected decarboxy-compound. This acid had an ultra-violet spectrum characteristic of an αβ-unsaturated acid. Its methyl ester could be acetylated to give both a monoacetate and a diacetate. Ozonolysis of the latter gave the same methyl ketone (III) as is obtained from the ozonolysis of both the diacetate of the decarboxylated acid (II) and methyl *iso*polyporenate diacetate (Halsall, Hodges, and Jones, *loc. cit.*). The acid must therefore be a geometrical isomer of *iso*polyporenic acid A. It has been given the trivial name, ψ-polyporenic acid A. The *iso*- and ψ-acids must each be represented by one of the two structures (XII) and (XIII) but it has not been possible to decide conclusively which is which, although, as indicated below, it is likely that (XII) represents the *iso*-acid. To distinguish systematically between *iso*-polyporenic acid A and ψ-polyporenic acid A, the former is designated as 3α : 12α-dihydroxy-eburico-8 : 24-dien-26-oic acid and the latter as 3α : 12α-dihydroxyeburico-8 : 24-dien-27-oic acid.

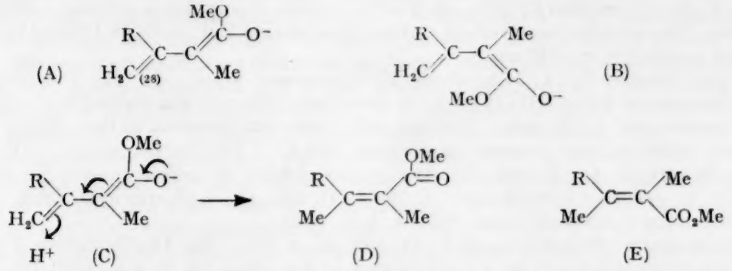
ψ-Polyporenic acid A was only obtained from "polyporenic acid A" prepared by hydrolysis of methyl polyporenate. It was not formed when pure acid A (obtained from the fungus



extract without methylation and hydrolysis) was decarboxylated, although when this acid was methylated, the resulting ester hydrolysed, and the hydrolysis product decarboxylated some ψ-polyporenic acid A was again isolated. It has already been shown that during the hydrolysis of methyl polyporenate A, methyl *iso*polyporenate A is formed (Halsall, Hodges, and Jones, *loc. cit.*). The formation of the ψ-acid is best explained by assuming that the hydrolysis product from methyl polyporenate A contained, in addition to acid A, some *iso*polyporenic acid A formed by hydrolysis of methyl *iso*polyporenate, and that the *iso*-acid is thermally isomerised to the ψ-acid.

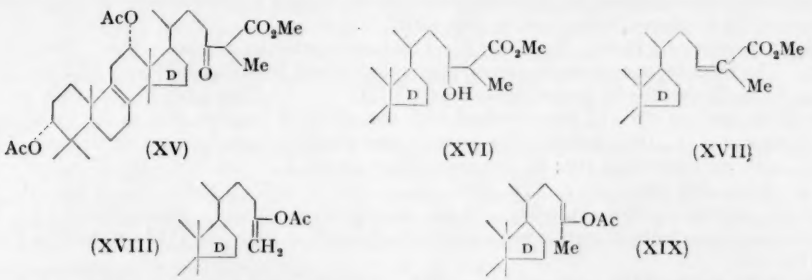
It is likely that *iso*polyporenic acid A has structure (XII) for the following reasons. When methyl polyporenate A is isomerised to methyl *iso*polyporenate A the intermediate ion in the reaction will exist mainly in the *transoid* form (A) rather than in the *cisoid* form (B) since the repulsion between the partial negative charges on the $C_{(28)}$ carbon atom and the carbonyl oxygen will be less in (A) than in (B). If proton attack occurs at $C_{(28)}$ to complete the isomerisation (cf. C) then the spatial distribution of atoms represented by (A) should also be present in methyl *iso*polyporenate A (cf. D). Structure (D) has the two largest groups *cis* to one another and therefore would be expected to be slightly less stable than structure (E). If methyl *iso*polyporenate A is represented by (D) then (E) must be methyl ψ-poly-

porenate A. The thermal isomerisation of the *iso*- to the *ψ*-acid is in agreement with this conclusion as it corresponds to the isomerisation of the less stable (D) to the more stable (E).



Although the relationship between polyporenic acid A and lanosterol was established by the formation from both of (VIII) as described above, our original intention had been to establish a relationship by the conversion of polyporenic acid A into a derivative of (XIV), which had already been prepared from lanosterol (Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, **1952**, **35**, 497). The formation of C_{27} acid derivatives was attempted by three different routes. The first was the oxidation of the methyl triketone (VIII) with sodium hypobromite or sodium hypoiodite, but both reagents failed to yield any acidic products.

The second route involved the ozonolysis of methyl polyporenate A diacetate to the β-oxo-ester (XV). This was reduced to the β-hydroxy-ester (XVI) with sodium borohydride, but an attempt by heating with acetic anhydride to dehydrate (XVI) to the αβ-unsaturated ester (XVII), which would have given a C_{27} acid on ozonolysis, gave only an uncrystallisable gum.



Finally, attempts were made to prepare from the methyl ketone (IV) the enol acetate (XVIII), ozonolysis of which would give the required C_{27} acid structure. When (III) was heated under reflux for 15 hours in chloroform with dimethylaniline and acetyl chloride a mixture of the enol acetate (XVIII) and the isomeric acetate (XIX) was obtained. The latter compound was the only product when the above reagents were heated under reflux for 3 days and also when the methyl ketone (III) was acetylated with *iso*propenyl acetate. Ozonolysis of the mixture of enol acetates gave the required C_{27} acid but the yield by this route did not encourage us to make use of it further.

Experimental

Rotations were determined in chloroform at room temperature unless otherwise stated. M. p.s were determined on a Kofler block and are corrected. Alumina of activity I—II was employed for all chromatograms, and the light petroleum used for elution had b. p. 60—80°. Crystallisations were from methanol unless stated otherwise.

3α : 12α-*Diacetoxy*-7 : 24-*dioxo*-26 : 27-*bisnorlanost*-8-*ene* (IV).—3α : 12α-Diacetoxy-24-oxo-26 : 27-bisnorlanost-8-ene (III) (Halsall, Hodges, and Jones, *loc. cit.*) (500 mg.) in acetic acid

(25 c.c.) was treated with chromic acid (225 mg.) at 80—90° for 10 min. Dilution with water and ether-extraction yielded a product which was adsorbed from benzene on alumina (50 g.). The fraction eluted with benzene–ether (9 : 1) gave 3α : 12α-*diacetoxy*-7 : 24-*dioxo*-26 : 27-*bisnorlanost*-8-*ene* as needles (330 mg.), m. p. 228—230°, $[\alpha]_D$ +73° (*c*, 0·71) (Found: C, 72·65; H, 9·4. $C_{32}H_{48}O_6$ requires C, 72·7; H, 9·15%). Light absorption in ethanol: Max., 2540 Å; ε = 9800. The infra-red spectrum in carbon tetrachloride had bands at 1735—1745 and 1673 cm.$^{-1}$ and a shoulder at 1730 cm.$^{-1}$.

3α : 12α-*Diacetoxy*-7 : 11 : 24-*trioxo*-26 : 27-*bisnorlanost*-8-*ene*.—3α : 12α-Diacetoxy-24-oxo-26 : 27-bisnorlanost-8-ene (III) (1·06 g.) in acetic acid (45 c.c.) was treated with chromic acid (1·85 g.) at 80—90° for 90 min. Dilution with water and ether-extraction yielded a product which was adsorbed from benzene on alumina (100 g.). The fraction eluted with ether gave 3α : 12α-*diacetoxy*-7 : 11 : 24-*trioxo*-26 : 27-*bisnorlanost*-8-*ene* as yellow prisms (65 mg.), m. p. 201—203°, $[\alpha]_D$ +94° (*c*, 0·63) (Found: C, 70·55; H, 8·5. $C_{32}H_{46}O_7$ requires C, 70·8; H, 8·55%). Light absorption in ethanol: Max., 2730 Å; ε = 7300.

7 : 24-*Dioxo*-26 : 27-*bisnorlanosta*-8 : 11-*dien*-3α-*ol* (V).—3α : 12α-Diacetoxy-7 : 24-dioxo-26 : 27-bisnorlanost-8-ene (1·61 g.) was heated under reflux for 30 min. with 1% methanolic potassium hydroxide (160 c.c.). Dilution with water and ether-extraction afforded a product which was adsorbed from benzene on alumina (150 g.). Elution with benzene–ether (3 : 2) yielded a fraction, giving 7 : 24-*dioxo*-26 : 27-*bisnorlanosta*-8 : 11-*dien*-3α-*ol* as plates (1·013 g.), m. p. 204—205°, $[\alpha]_D$ −4° (*c*, 1·0) (Found: C, 78·7; H, 9·85. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%). Light absorption in ethanol: Max., 3180 Å; ε = 8450. The infra-red spectrum in carbon tetrachloride had bands at 1657 and 1718 cm.$^{-1}$.

Zinc-dust Reduction of 7 : 24-*Dioxo*-26 : 27-*bisnorlanosta*-8 : 11-*dien*-3α-*ol* (V).—Zinc dust (4 g.) was added in small portions during 2 hr. to a boiling solution of 7 : 24-dioxo-26 : 27-bisnorlanosta-8 : 11-dien-3α-ol (1·96 g.) in acetic acid (200 c.c.). Dilution with water and ether-extraction afforded a product which was adsorbed from benzene on alumina (150 g.). Elution with benzene–ether (19 : 1) yielded a fraction which gave 7 : 24-*dioxo*-26 : 27-*bisnorlanost*-8-*en*-3α-*yl acetate* as plates (146 mg.), m. p. 159—161°, $[\alpha]_D$ −42° (*c*, 1·21) (Found: C, 76·85; H, 9·9. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption in ethanol: Max., 2540 Å; ε = 8900. Further elution with benzene–ether (1 : 1) yielded a fraction which gave 7 : 24-*dioxo*-26 : 27-*bisnorlanost*-8-*en*-3α-*ol* (VII) as plates (1·05 g.), m. p. 195—197°, $[\alpha]_D$ 0° (*c*, 0·72) (Found: C, 78·75; H, 10·25. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Light absorption in ethanol: Max., 2540 Å; ε = 9700. The infra-red spectrum in carbon tetrachloride had bands at 1665 and 1719 cm.$^{-1}$.

3 : 7 : 24-*Trioxo*-26 : 27-*bisnorlanost*-8-*ene* (VIII).—7 : 24-Dioxo-26 : 27-lanost-8-en-3α-ol (1·05 g.) in acetone (30 c.c.) was oxidised with chromic acid solution (8N) in the usual manner (cf. Bowers *et al.* *J.*, 1953, 2555). The product was adsorbed from benzene on alumina (100 g.), eluted with benzene–ether (19 : 1), and crystallised giving 3 : 7 : 24-*trioxo*-26 : 27-*bisnorlanost*-8-*ene* as plates (894 mg.), m. p. 171—172°, $[\alpha]_D$ +13° (*c*, 0·87) (Found: C, 78·65; H, 10·05. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%). Light absorption in ethanol: Max., 2530 Å; ε = 8900. The infra-red spectrum in carbon tetrachloride had bands at 1670 and 1713 cm.$^{-1}$ and a shoulder at 1718 cm.$^{-1}$.

3 : 24-*Dioxo*-26 : 27-*bisnorlanost*-8-*ene* (XI).—"Isocholesteryl acetate" (8·4 g.) in ethyl acetate (200 c.c.) was treated with ozonized oxygen (6%) for 6½ hr. The solution was then washed repeatedly with ferrous sulphate solution. The residue obtained by evaporation of the ethyl acetate was dissolved in ether (500 c.c.) and heated under reflux with methylmagnesium iodide (15 g.) in ether (300 c.c.) for 30 min. From the mixture the crude diol was isolated in the usual manner and was oxidised in acetone (200 c.c.) with chromic acid solution (8N). The neutral fraction formed was separated, adsorbed from benzene–light petroleum (1 : 1) on alumina (500 g.), and eluted with benzene–ether (19 : 1) giving 3 : 24-*dioxo*-26 : 27-*bisnorlanost*-8-*ene* as platelets (1·97 g.), m. p. 178—184°, $[\alpha]_D$ +77° (*c*, 0·77) (Found: C, 81·55; H, 10·8. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%).

Oxidation of 3 : 24-*Dioxo*-26 : 27-*bisnorlanost*-8-*ene from* "*Isocholesteryl Acetate*."—The diketone (850 mg.) in acetic acid (50 c.c.) was oxidised with chromic acid (350 mg.) at 80—90° for 13 min. Dilution with water and extraction with ether afforded a product which was adsorbed from benzene on alumina (100 g.). Elution with benzene–ether (1 : 1) yielded a fraction which on crystallisation gave 3 : 7 : 24-trioxo-26 : 27-bisnorlanost-8-ene as plates (391 mg.), m. p. 171·5—173° (undepressed on admixture with a sample prepared from polyporenic acid A), $[\alpha]_D$ +12° (*c*, 0·48). Light absorption in ethanol: Max., 2540 Å; ε = 8600. The infra-red spectrum in carbon tetrachloride was identical with that of a sample prepared from polyporenic acid A.

ψ-Polyporenic Acid A (*3α : 12α-Dihydroxyeburico-8 : 24-dien-27-oic Acid*).—Methyl polyporenate A (37 g.) was heated under reflux for 10 hr. with methanolic potassium hydroxide (3%; 300 c.c.). The solution was then diluted with water and acidified with acetic acid. The precipitated acid was crystallised once from aqueous *iso*propanol, giving a mixture of polyporenic acid A and *iso*polyporenic acid A (30 g.). The mixed acids (40 g.) were kept at 220° for 1 hr. under nitrogen, and the product was then separated into an acidic (7 g.) and a neutral fraction. Repeated crystallisation of the former from aqueous methanol, *iso*propanol, dioxan, and acetic acid gave *ψ-polyporenic acid A* (*3α : 12α-dihydroxyeburico-8 : 24-dien-27-oic acid*) as fine needles, m. p. 265—266°, $[\alpha]_D$ +51° (*c*, 1·0 in pyridine) (Found: C, 76·7; H, 10·45. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%). Light absorption in ethanol: Max., 2260 Å; ε = 10,500. Methylation of the acid with ethereal diazomethane in the usual manner gave *methyl ψ-polyporenate A* (*methyl 3α : 12α-dihydroxyeburico-8 : 24-dien-27-oate*) as needles (from nitromethane), m. p. 180—181°, $[\alpha]_D$ +65° (*c*, 0·97) (Found: C, 76·5; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). Light absorption in ethanol: Max., 2260 Å; ε = 10,800.

Methyl ψ-Polyporenate A Diacetate.—Methyl ψ-polyporenate A (300 mg.) was heated under reflux for 1 hr. with acetic anhydride (5 c.c.) and sodium acetate (100 mg.). The product was adsorbed from benzene on alumina (30 g.) and eluted with benzene–ether (9 : 1), giving *methyl ψ-polyporenate A diacetate* (*methyl 3α : 12α-diacetoxyeburico-8 : 24-dien-27-oate*) as needles (260 mg.), m. p. 154—155°, $[\alpha]_D$ +68° (*c*, 1·58) (Found: C, 73·85; H, 9·75. $C_{36}H_{56}O_6$ requires C, 73·95; H, 9·65%). Light absorption in ethanol: Max., 2260 Å; ε = 10,100.

Methyl ψ-Polyporenate A Monoacetate.—Methyl ψ-polyporenate A (200 mg.) in pyridine (3 c.c.) was treated with acetic anhydride (1 c.c.) and kept at 20° for 3 days. The product was adsorbed from benzene on alumina (20 g.) and eluted with benzene–ether (3 : 2), giving *methyl ψ-polyporenate A monoacetate* (*methyl 3α-acetoxy-12α-hydroxyeburico-8 : 24-dien-27-oate*) as needles (152 mg.), m. p. 164·5—165·5°, $[\alpha]_D$ +21° (*c*, 1·19) (Found: C, 75·45; H, 10·2. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·05%). Light absorption in ethanol: Max., 2260 Å; ε = 10,900. After one year the monoacetate melted at 190—192°. This melting point was undepressed on admixture with a sample of the monoacetate which was prepared by the same method in a later experiment and crystallised as plates.

Oxidation of Methyl ψ-Polyporenate A.—Methyl ψ-polyporenate A (250 mg.) in acetone (20 c.c.) was oxidised with chromic acid (8N) in sulphuric acid (25% v/v) at 30°. The product was adsorbed from benzene on alumina (25 g.) and eluted with benzene–ether (1 : 1), giving *methyl 3 : 12-dioxoeburico-8 : 24-dien-27-oate* as needles (206 mg.), m. p. 191—192°, $[\alpha]_D$ +94° (*c*, 1·49) (Found: C, 77·35; H, 9·65. $C_{32}H_{48}O_4$ requires C, 77·35; H, 9·75%). Light absorption in ethanol: Max., 2260 Å; ε = 11,150.

Ozonolysis of Methyl ψ-Polyporenate A Diacetate.—Methyl ψ-polyporenate A diacetate (380 mg.) in acetic acid (10 c.c.) was treated with ozonised oxygen for 20 min. The solution was then heated under reflux with water (20 c.c.) for 10 min. The product, isolated by ether-extraction, was adsorbed from benzene on alumina (30 g.), and eluted with ether, giving *3α : 12α-diacetoxy-24-oxo-26 : 27-bisnorlanost-8-ene* (III) as needles (200 mg.), m. p. 199—201° (undepressed on admixture with an authentic sample), $[\alpha]_D$ +82° (*c*, 0·50).

Attempted Oxidation of 26 : 27-Bisnorlanost-8-ene-3 : 7 : 24-trione (VIII).—*3 : 7 : 24-Trioxo-26 : 27-bisnorlanost-8-ene* (300 mg.) in methanol (50 c.c.) was treated with a mixture of bromine (300 mg.) and sodium hydroxide (250 mg.) in water (10 c.c.). After 24 hr. the solution was diluted with water, extracted with ether, acidified with acetic acid, and re-extracted with ether. No acidic fraction was obtained. Attempts to oxidise the triketone to a C_{27}-acid with sodium hypoiodite were also unsuccessful.

Ozonolysis of Methyl Polyporenate A Diacetate [*Methyl 3α : 12α-Diacetoxyeburico-8 : 24(28)-dien-26-oate*].—Methyl polyporenate A diacetate (2·5 g.) in acetic acid (40 c.c.) was treated with ozonised oxygen (6%) for 80 min. The solution was then heated under reflux with water (80 c.c.) for 10 min. The product, isolated with ether, was adsorbed from benzene–light petroleum (6 : 4) on alumina (200 g.) and eluted with benzene, giving *methyl 3α : 12α-diacetoxy-24-oxolanost-8-en-26-oate* (XV) as needles (1·50 g.), m. p. 142—143°, $[\alpha]_D$ +104° (*c*, 0·83) (Found: C, 72·0; H, 9·1. $C_{35}H_{54}O_7$ requires C, 71·65; H, 9·3%). Light absorption in ethanol: Max., 2480 Å; ε = 5900. Light absorption in ethanol with a trace of alkali present: Max., 2860 Å; ε = 14,400. The infra-red spectrum in carbon tetrachloride exhibited a band at 1733 cm.$^{-1}$ with a shoulder at 1740 cm.$^{-1}$.

Reduction of Methyl 3α : 12α-Diacetoxy-24-oxolanost-8-en-26-oate (XV) *with Sodium Borohydride*.—The β-keto-ester (586 mg.) in dioxan (35 c.c.) was treated with sodium borohydride (50 mg.) in water (5 c.c.) and kept at 20° for 1 hr. The product, isolated with ether, was adsorbed

from benzene on alumina (50 g.) and eluted with ether, giving *methyl* 3α : 12α-*diacetoxy*-24-*hydroxylanost*-8-*en*-26-*oate* as needles (261 mg.), m. p. 124—125°, $[\alpha]_D$ +76° (*c*, 0·93) (Found : C, 70·9; H, 9·5. $C_{35}H_{56}O_7$ requires C, 71·4; H, 9·6%).

Attempted Dehydration of Methyl 3α : 12α-*Diacetoxy*-24-*hydroxylanost*-8-*en*-26-*oate*.—The ester (115 mg.) was heated under reflux with acetic anhydride (5 c.c.) for 1 hr. The product, isolated with ether, was adsorbed from light petroleum on alumina (10 g.) and eluted with benzene, giving an uncrystallisable gum (102 mg.). Light absorption in ethanol : Max., 2480 Å; ε = *ca.* 700.

Methyl 3α : 12α-*Dihydroxy*-24-*oxolanost*-8-*en*-26-*oate*.—Methyl polyporenate A (3·0 g.) in acetic acid (50 c.c.) was treated with ozonised oxygen (6%) for 3 hr. The solution was then heated under reflux with water (100 c.c.) for 10 min. The product, isolated with ether, was adsorbed from benzene on alumina deactivated with water (5%), and eluted with benzene–ether (4 : 1), giving *methyl* 3α : 12α-*dihydroxy*-24-*oxolanost*-8-*en*-26-*oate* as fine needles (920 mg.) (from nitromethane), m. p. 115—116°, $[\alpha]_D$ +64° (*c*, 1·10) (Found : C, 74·3; H, 10·2. $C_{31}H_{50}O_5$ requires C, 74·05; H, 10·05%). Light absorption in ethanol : Max., 2560 Å; ε = 240. Light absorption in ethanol with a trace of alkali present : Max., 2860 Å; ε = 14,500.

Enol Acetylation of 3α : 12α-*Diacetoxy*-26 : 27-*bisnorlanost*-8-*en*-24-*one* (III).—(*a*) 3α : 12α-Diacetoxy-26 : 27-bisnorlanost-8-en-24-one (500 mg.) in chloroform (5 c.c.) was heated under reflux with dry dimethylaniline (6 c.c.) and acetyl chloride (4 c.c.) for 15 hr. The product, isolated in the usual manner, was adsorbed from light petroleum on alumina (50 g.) and eluted with benzene, giving crystals (110 mg.), m. p. 114—120°, of a mixture of 3α : 12α : 24-triacetoxy-26 : 27-bisnorlanosta-8 : 23-diene (XIX) and 3α : 12α : 24-triacetoxy-26 : 27-bisnorlanosta-8 : 24-diene (XVIII). The infra-red spectrum in carbon tetrachloride had bands at 1735, 1669, and 873 cm.$^{-1}$. The band at 873 cm.$^{-1}$ indicates the presence of the grouping $>C = CH_2$.

(*b*) 3α : 12α-Diacetoxy-26 : 27-bisnorlanost-8-en-24-one (2·4 g.) in chloroform (13 c.c.) was heated under reflux for 3 days with dimethylaniline (15 c.c.) and acetyl chloride (10 c.c.). The product, isolated in the usual manner, was adsorbed from light petroleum on alumina (200 g.) and eluted with benzene–light petroleum (3 : 2), giving 3α : 12α : 24-*triacetoxy*-26 : 27-*bisnorlanosta*-8 : 23-*diene* (XX) as needles (920 mg.) (repeated crystallisation), m. p. 148—150°, $[\alpha]_D$ +64° (*c*, 0·93) (Found : C, 73·65; H, 9·4. $C_{34}H_{52}O_6$ requires C, 73·35; H, 9·4%). Acetylation with *iso*propenyl acetate yielded the same product. The infra-red spectrum in carbon tetrachloride had a band at 1735 cm.$^{-1}$.

Methyl 3α : 12α-*Diacetoxy*-4 : 4 : 14α-*trimethyl*allo*chol*-8-*en*-24-*oate*.—The mixed enol acetates (443 mg.; m. p. 114—120°), described in the cognate paragraph above, in ethyl acetate were treated with ozonised oxygen (6%) for 20 min. The solution was then washed with ferrous sulphate solution and separated into an acid (190 mg.) and a neutral fraction. The former was methylated with ethereal diazomethane, and the resulting ester was adsorbed from benzene on alumina (20 g.) and eluted with benzene–ether (1 : 1), giving *methyl* 3α : 12α-*diacetoxy*-4 : 4 : 14α-*trimethyl*allo*chol*-8-*en*-24-*oate* as plates (85 mg.), m. p. 196—198°, $[\alpha]_D$ +88° (*c*, 0·89) (Found : C, 72·3; H, 9·45. $C_{32}H_{50}O_6$ requires C, 72·4; H, 9·5%).

3α : 12α-*Dihydroxy*-26 : 27-*bisnorlanost*-8-*en*-24-*one*.—3α : 12α-Diacetoxy-26 : 27-bisnorlanost-8-en-24-one (1·58 g.) was heated under reflux with 1% methanolic potassium hydroxide (50 c.c.) for 18 hr. The product, isolated in the usual manner, was adsorbed from benzene on alumina (150 g.) and eluted with ether–methanol (19 : 1), giving 3α : 12α-*dihydroxy*-26 : 27-*bisnorlanost*-8-*en*-24-*one* as plates (726 mg.), m. p. 209—210·5°, $[\alpha]_D$ +73° (*c*, 0·99) (Found : C, 78·45; H, 10·7. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·75%). The infra-red spectrum in carbon disulphide had a band at 1713 cm.$^{-1}$.

Methyl 4 : 4 : 14α-*Trimethyl*-3-*oxo*allo*chol*-8-*en*-24-*oate*.—" Isocholesterol " (3·0 g.) in acetic acid (200 c.c.) was treated with ozonised oxygen for 2½ hr. The product, isolated by extraction with ether, was oxidised in acetone (200 c.c.) with chromic acid solution (8N) in the usual way. The acid formed (1·18 g.) was separated and methylated with ethereal diazomethane, and the product adsorbed from benzene–light petroleum (4 : 1) on alumina (150 g.). Elution with benzene gave *methyl* 4 : 4 : 14α-*trimethyl*-3-*oxo*allo*chol*-8-*en*-24-*oate* as needles (720 mg.), m. p. 141—143°, $[\alpha]_D$ +76° (*c*, 0·97) (Found : C, 78·0; H, 10·45. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%).

Methyl 4 : 4 : 14α-*Trimethyl*-3 : 7-*dioxo*allo*chol*-8-*en*-24-*oate*.—Methyl 4 : 4 : 14α-trimethyl-3-oxo*allo*chol-8-en-24-oate (400 mg.) in acetic acid (35 c.c.) was treated with chromic acid (180 mg.) and kept at 80—90° for 10 min. Extraction with ether yielded a product which was adsorbed from benzene on alumina (40 g.). Elution with benzene–ether (9 : 1) gave *methyl* 4 : 4 : 14α-*trimethyl*-3 : 7-*dioxo*allo*chol*-8-*en*-24-*oate* as needles (271 mg.), m. p. 154—155°,

$[\alpha]_D$ +5° (*c*, 0·78) (Found: C, 75·8; H, 9·6. $C_{28}H_{42}O_4$ requires C, 75·95; H, 9·55%). Light absorption in ethanol: Max., 2520 Å; ε = 8,800.

The authors thank Professor E. R. H. Jones, F.R.S., for his interest and advice. One of the authors (R. H.) is indebted to the University of Manchester for a Research Studentship and to the Royal Commissioners of the 1851 Exhibition for the award of an Overseas Scholarship. Thanks are also proffered to Mr. E. S. Morton and Mr. H. Swift for the microanalyses.

THE UNIVERSITY, MANCHESTER 13. [*Received, February 23rd*, 1954.]

Nitramines and Nitramides. Part VII. The Irreversible Decomposition of Nitroguanidine and of Nitrourea by Sulphuric Acid.*

By C. HOLSTEAD and ALEX. H. LAMBERTON.

[Reprint Order No. 5183.]

The decomposition of nitroguanidine and of nitrourea by means of sulphuric acid at 55° has been investigated quantitatively. It appears that nitroguanidine (I) is converted into urea (II). The final products depend, however, upon the concentration of the sulphuric acid, since nitric acid and the urea formed from nitroguanidine may be removed by combination and the subsequent decomposition of nitrourea. In this event the major end-product is guanidine. The behaviour of nitrourea (investigated separately) correlates well with, and elucidates, the behaviour of nitroguanidine.

MENTION has already been made (Part V, *J.*, 1953, 3341) of the irreversible decomposition of certain *N*-nitro-compounds in sulphuric acid–water media. The behaviour of nitroguanidine and of nitrourea has now been examined, in acid of 83·6—99·3% w/w concentration, at a temperature (55°) sufficiently high to produce complete decomposition in a reasonable period. The solutions, initially 0·2M, were made from guanidine and urea nitrates respectively. Since the nitration–denitration equilibrium was established rapidly in the conditions employed, this procedure was equivalent to the use of nitroguanidine or nitrourea as initial materials.

It was found that urea, guanidine (added as guanidine sulphate), and nitric acid (added as ammonium nitrate) were unaffected by treatment which brought about, in the same time, complete decomposition of guanidine nitrate and *ca.* 75% decomposition of urea nitrate. The decomposition of the latter substances must therefore occur through the *N*-nitro-compounds.

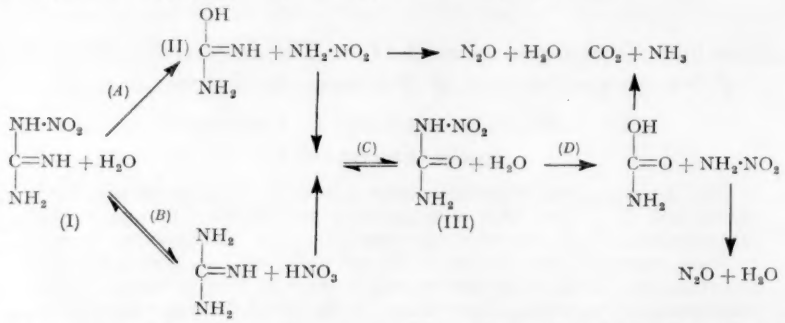
The reaction may be formulated (without, for the moment, any implication regarding the precise mechanism) as the hydrolysis $X{\cdot}NH{\cdot}NO_2 + H_2O \longrightarrow X{\cdot}OH + NH_2{\cdot}NO_2$. It may be admitted that no direct evidence of the formation of nitramine has been obtained; but a colourless gas was evolved during the decompositions, and we found that the addition of nitramine to 99·3% w/w sulphuric acid at 5° led to effervescence and a residual solution containing a negligible quantity of nitric acid. Davis (*J. Amer. Chem. Soc.*, 1922, **44**, 868) has shown that (at higher temperatures) in the Kjeldahl process nitroguanidine reacts according to the equation $NH_2{\cdot}C(NH){\cdot}NH{\cdot}NO_2 + H_2O \longrightarrow CO_2 + N_2O + 2NH_3$; he also (Davis and Blanchard, *ibid.*, 1929, **51**, 1790) claimed the isolation of nitramine from a concentrated solution of nitrourea in sulphuric acid.

It appears that, in the conditions we used, nitroguanidine (I) is converted (reaction *A*) into urea (II). The formation of urea was first postulated on theoretical grounds, then confirmed by quantitative determination with urease, and finally proved by isolation of the xanthhydrol derivative. Since the nitroguanidine is at the same time in equilibrium with guanidine nitrate (reaction *B*), the urea formed in (*A*) is converted (reaction *C*) in part into nitrourea (III). This, in turn, suffers irreversible decomposition, presumably into carbamic acid and nitramine (reaction *D*). The end products are probably carbon dioxide and ammonium sulphate, formed either directly or by way of cyanic acid. We found that com-

* Part VI, *J.*, 1953, 3349.

plete decomposition of nitrourea by sulphuric acid yielded one molecular proportion of ammonia when the reaction mixture was made alkaline and distilled.

During the decomposition of nitroguanidine we determined the total nitric acid (free, and bound as $>N\cdot NO_2$), free nitric acid, guanidine, and urea. In 99·3% w/w sulphuric acid, the amounts of total nitric acid, free nitric acid, and guanidine fell, whilst the urea content rose to, finally, a 75% yield. In 88·1 and 83·6% w/w sulphuric acid, total and free nitric acid concentrations fell, whilst that of urea rose only to 11 and 5% yields, respectively; guanidine (43 and 46% yields, respectively) was the major product.



The facts reported in the preceding paragraph correlate well with the behaviour of urea. Urea nitrate (equivalent, in sulphuric acid, to nitrourea) was found to be almost stable in 99·3% w/w sulphuric acid at 55°: the decomposition is much slower than that of guanidine nitrate. It follows that, for guanidine nitrate under these conditions, most of the nitric acid is removed by reactions *B* and *A*, and very little by reactions *C* and *D*; and, as found experimentally, urea is the major product. In 88·1 or 83·6% w/w sulphuric acid we found the decomposition of urea nitrate to be much faster than that of guanidine nitrate. Therefore, for guanidine nitrate under these conditions, there is also considerable loss of nitric acid by reactions *C* and *D*; the supply of nitric acid runs out, leaving some guanidine behind. In 88·1 and 83·6% w/w sulphuric acid equilibrium *B* lies mainly to the left, and the rise in free guanidine content must be due to denitration of (I) as the reactions proceed. The relatively slow decomposition of urea nitrate in 99·3% w/w sulphuric acid is in part—but probably not wholly, as analysis of the results already presented (Part V, *loc. cit.*) shows—due to the fact that equilibrium *C* lies almost completely to the left. Such a solution contains very little nitrourea which can suffer decomposition.

The observed yield (46%) of guanidine obtained by complete irreversible decomposition of nitroguanidine (in 83·6% w/w sulphuric acid) is in fact high. Loss of nitric acid by reactions *C* and *D* can only occur after urea has been formed, and nitric acid lost, by reaction *A*: the maximum possible yield of guanidine on the basis of these equations is 50%.

We have made similar measurements in 94·7% w/w sulphuric acid. These show that this concentration is approximately the boundary between predominance of the route yielding urea, and the route yielding guanidine.

It may be added that (i) the yields obtained from nitroguanidine are not fully quantitative, especially in sulphuric acid of >90% w/w concentration, and therefore some minor reactions are possibly undiscovered; and (ii) the fall in free nitric acid concentration, in the case of nitrourea, is approximately of the second order—a result consonant with a decomposition of the first order with respect to nitrourea. These observations are dealt with more fully in the Experimental section.

Experimental

The solutions were made up, and analysed for free nitric acid in the presence of *N*-nitrocompounds, in the manner previously described (Part V, *loc. cit.*; Simkins and Williams, *J.*, 1952, 3086). Times (*t*, in min.) were measured from the initial mixing, and the solutions were made up with acid previously warmed to 55°. The sampling pipettes were calibrated by

weight delivered at 55°, and all molarities reported are those which would have occurred in the solution after sudden cooling, without chemical change, to 25°. Owing to thermal expansion, the true molarities at 55° must have been slightly smaller.

" Total " Nitric Acid.—A 3-ml. sample was pipetted into 98% sulphuric acid (100 ml.) in a 250-ml. wide-mouthed flask, and titrated directly with ferrous ammonium sulphate (*ca.* 0·07N in 30% sulphuric acid) to a potentiometric end-point, under an atmosphere of carbon dioxide (Treadwell and Vontobel, *Helv. Chim. Acta*, 1937, **20**, 573; and especially Cottrell, MacInnes, and Paterson, *Analyst*, 1946, **71**, 207). We used the apparatus of Cottrell *et al.* (*loc. cit.*), who found that nitroguanidine thus liberated nitric acid quantitatively; and we found nitrourea to behave in the same way. The analysis was accurate to ±0·0005M-nitric acid.

Guanidine.—A 5-ml. sample was pipetted into 175 ml. of a stock solution of picric acid (1·960 g./l.; saturated with guanidine picrate at 0°). Sodium hydroxide (10 ml. of 50%, w/w) was added, and the partly neutralised solution kept overnight in an ice-chest. Aqueous guanidine carbonate (1 ml. of concentration 7·203 g./l.) was then added to form nuclei, and the precipitation completed by stirring at 0° for 30 min. The precipitate was collected in a sintered-glass crucible, washed with ice-cold water (50 ml.; saturated with guanidine picrate at 0°), and dried in a steam-oven. Simpler methods, and the use of ammonium picrate solutions, were found to be inapplicable on account of the relatively large initial quantity of sulphuric acid. A variable empirical correction, related to the weight of guanidine picrate precipitated, was necessary on account of (*a*) the solubility of guanidine picrate, and (*b*) the addition of guanidine carbonate (equiv. to 23 mg. of picrate) to seed the solution. Our correction graph was based on the following figures (in each case the observed weight of precipitate in mg. is followed by the net correction in mg.): 242, 23; 197, 11; 147, 3; 91, 1; 39, −4; 4, −4. The analysis was accurate to ±0·002M-guanidine.

Urea.—A 3-ml. sample, pipetted into water (20 ml.), was made slightly alkaline with sodium hydroxide solution (50% w/w) and finally neutralised with 0·05N-hydrochloric acid, a mixed methyl-red–bromocresol-green indicator being used. Three 25-mg. tablets of urease (Hynson, Westcolt, and Dunning) were ground in water (5 ml.), neutralised (hydrochloric acid and mixed indicator), and added to the urea solution. The liberated ammonium carbonate was titrated from time to time during incubation (20 min. at 45°), and complete decomposition was assured by setting the stoppered flask aside overnight at 45° before the final addition of hydrochloric acid was made. The analysis was accurate to ±0·001M-urea.

Rapidity of Equilibrium at 55°.—Solutions (0·2M) were made up in 83·6% w/w sulphuric acid at 55°, and free nitric acid was determined t min. after mixture with the following results: guanidine nitrate, $t = 9$, $HNO_3 = 0·032$M; nitroguanidine, $t = 9$, $HNO_3 = 0·031$M; urea nitrate, $t = 10$, $HNO_3 = 0·107$M; nitrourea, $t = 9$, $HNO_3 = 0·102$M. In the urea experiments considerable decomposition (see Expt. 8) has already occurred, but the approximate agreement indicates that the speed of equilibration does not seriously influence the observed course of decomposition. In more concentrated acid equilibrium is established even more rapidly.

Decomposition of Guanidine Nitrate and of Urea Nitrate.—The principal results are recorded in Tables 1 and 2.

Stability of Urea, Guanidine, and Nitric Acid in 99·3% w/w Sulphuric Acid at 55°.—Separate solutions of urea, guanidine sulphate, and ammonium nitrate (all 0·2M) were made up; urea, guanidine, and free nitric acid were, respectively, found to be invariant (0·2M to within experimental error) up to 48 hr. Davis and Abrams (*J. Amer. Chem. Soc.*, 1925, **47**, 1043) suggest that, at high temperatures, ammonium nitrate is decomposed by sulphuric acid to yield (*via* nitramine) nitrous oxide and water; no sign of such a reaction was found at 55°.

Decomposition of Nitramine in 99·3% w/w Sulphuric Acid.—Nitramine (sufficient to make a 0·2M-solution) was added portionwise to the acid at 0° to 5°. Vigorous effervescence occurred, and the residual solution was only 0·003M in free or total nitric acid. This small quantity may well have come from nitrourethane, a possible impurity in samples of nitramine.

Isolation of the Xanthhydrol Derivative of Urea.—A 2M-solution of guanidine nitrate in 99·3% w/w sulphuric acid was kept for 24 hr. at 55°. A sample (1 ml.) was diluted with water (5 ml.) and cooled; subsequent addition of glacial acetic acid (3·5 ml.) and xanthhydrol (5 ml. of 10% solution in methyl alcohol) gave a precipitate which was collected, washed with methyl alcohol, and dried; it had m. p. 273°, not depressed by mixture with the authentic urea derivative.

Analysis of the Yields of Guanidine and Urea in Relation to the Fall in Nitric Acid Concentration.—On the basis of the equations presented, nitric acid can only be removed from the solutions through decomposition of nitroguanidine and/or nitrourea: each molecule of potential nitric acid which disappears removes at the same time one potential guanidine or urea molecule. The

TABLE 1. *Decomposition of guanidine nitrate* (0·2M *at* 25°) *in sulphuric acid–water mixtures at* 55° ± 0·2°.

	Total [HNO_3]		Free [HNO_3]		[Guanidine]		[Urea]	
	t (min.)	M	*t* (min.)	M	*t* (min.)	M	*t* (min.)	M
Expt. 1. H_2SO_4, 99·3%, w/w.	50	0·138	14	0·143	25	0·138	30	0·039
	97	0·108	75	0·104	83	0·100	91	0·081
	204	0·071	183	0·066	191	0·069	197	0·113
	300	0·053	275	0·051	285	0·055	292	0·126
	405	0·040	388	0·038	394	0·043	400	0·134
	638	0·025	619	0·023	626	0·029	632	0·143
	1,393	0·008	1,369	0·007	1,378	0·019	1,384	0·149
	2,815	Nil	2,830	Nil	2,838	0·013	2,845	0·151
Expt. 3. H_2SO_4, 94·7%, w/w.	34	0·163	11	0·068	16	0·065	27	0·024
	87	0·112	64	0·051	73	0·060	80	0·049
	188	0·050	173	0·023	178	0·059	182	0·065
	281	0·023	262	0·011	269	0·058	275	0·068
	393	0·010	370	0·004	379	0·056	386	0·071
	1,440	Nil	1,446	Nil	1,450	0·054	1,457	0·072
Expt. 5. H_2SO_4, 88·1%, w/w.	28	0·189	13	0·018	21	0·017	18	0·004
	85	0·162	68	0·014	77	0·021	73	0·008
	206	0·116	183	0·007	198	0·035	189	0·011
	291	0·092	271	0·004	284	0·043	277	0·014
	411	0·066	392	0·001	404	0·049	397	0·018
	763	0·015	741	Nil	757	0·073	750	0·019
	1,622	0·002	1,495	Nil	1,509	0·085	1,501	0·022
Expt. 7. H_2SO_4, 83·6%, w/w.	38	0·196	16	0·031	25	0·029	28	0·003
	91	0·188	70	0·029	76	0·031	82	0·004
	268	0·164	241	0·023	250	0·035	258	0·005
	634	0·123	613	0·013	622	0·045	629	0·006
	1,357	0·069	1,330	0·005	1,340	0·064	1,350	0·008
	2,071	0·039	2,045	0·002	2,055	0·075	2,064	0·009
	4,253	0·007	4,224	Nil	4,234	0·090	4,243	0·010
	10,080	Nil	10,032	Nil	10,041	0·092	10,054	0·010

TABLE 2. *Decomposition of urea nitrate* (0·2M *at* 25°) *in sulphuric acid–water mixtures at* 55° ± 0·2°.

	Total [HNO_3]		Free [HNO_3]		[Urea]	
	t (min.)	M	*t* (min.)	M	*t* (min.)	M
Expt. 2. H_2SO_4, 99·3%, w/w.	25	0·193	14	0·192	18	0·193
	67	0·186	56	0·185	62	0·185
	190	0·168	163	0·169	172	0·165
	548	0·132	532	0·131	537	0·131
	1,382	0·091	1,360	0·091	1,370	0·093
	2,933	0·059	2,902	0·058	2,908	0·058
	4,493	0·043	4,475	0·041	4,483	0·043
Expt. 4. H_2SO_4, 94·7%, w/w.	19	0·139	10	0·156	14	0·150
	78	0·072	48	0·092	60	0·087
	133	0·050	111	0·055	119	0·056
	199	0·037	187	0·038	193	0·040
	398	0·020	386	0·020	392	0·023
	1,205	0·006	1,190	0·006	1,198	0·010
Expt. 6. H_2SO_4, 88·1%, w/w.	27	0·038	18	0·045	10	0·071
	58	0·017	50	0·017	43	0·026
	190	0·004	182	0·004	173	0·008
Expt. 8. H_2SO_4, 83·6%, w/w.	26	0·097	14	0·095	10	0·107
	49	0·048	43	0·048	37	0·058
	84	0·030	77	0·030	72	0·032
	157	0·016	152	0·015	146	0·017
	218	0·011	211	0·011	198	0·013

relation appears to be quantitative in the case of urea nitrate; the curves for free nitric acid and for urea are identical, showing that the removal of nitric acid does not either lag behind or precede the removal of urea; and therefore, apart from the unlikely contingency of two unknown reactions whose effects cancel each other, the decomposition products of nitrourea cannot react significantly with urea or nitric acid.

This is not the case with guanidine nitrate, even when allowance is made for the behaviour

of the urea formed. It is possible, at the end of the decomposition, when no significant proportion of the materials in question is " hidden " as *N*-nitro-compounds, to determine how much potential guanidine and potential urea have been destroyed. The sum of these should be the same as the total fall in nitric acid concentration, but is in fact smaller (Table 3). The difference of up to 12% seems much greater than possible errors in analysis, and presumably indicates the extent of side reactions.

TABLE 3. *Comparison of nitroguanidine and nitrourea decomposed with observed loss of nitric acid, for guanidine nitrate* (0·2M *at* 25°) *in sulphuric acid at* 55°. (*All values expressed as molarities at* 25°, *and calculated from observations made when decomposition was essentially complete.*)

	Sulphuric acid, % w/w.			
	99·3	94·7	88·1	83·6
Time of decomposition, hr.	47	24	25	167
A. Nitroguanidine decompd. = (0·2 − residual guanidine) = urea formed	0·187	0·146	0·115	0·108
B. Nitrourea decompd. = (urea formed − residual urea)	0·036	0·074	0·093	0·098
C. Theoretical loss of nitric acid (A + B)	0·223	0·220	0·208	0·206
D. Observed loss of nitric acid	0·200	0·200	0·198	0·200

Rate of Decomposition of Nitrourea.—When slow enough for accurate measurement, the rate was of the second order. From the equilibrium constant, $[\text{Nitrourea}][H_2O]/[\text{Urea}][HNO_3]$, and the fact that, even in 99% acid, $[H_2O]$ is essentially constant during the decomposition of 0·2M-urea nitrate, $[\text{Nitrourea}] \propto [\text{Urea}][HNO_3]$. Since urea and nitric acid were initially present in equimolar quantities, and if these disappear only through the decomposition of nitrourea, with elimination of equivalent quantities of bound urea and bound nitric acid, then $[\text{Urea}] = [HNO_3]$ at any stage; and $[\text{Nitrourea}] \propto [HNO_3]^2$. Counter-balancing side reactions are possible, but unlikely; the second-order fall of free nitric acid content supports the hypothesis of decomposition through the *N*-nitro-compound, and suggests a first-order rate with respect to nitrourea.

STAVELEY CHEMICAL LABORATORIES,
THE UNIVERSITY, SHEFFIELD, 3.

[*Received, March 6th,* 1954.]

Immunopolysaccharides. Part II. Structure of a* Betacoccus arabinosaceous *Dextran.*

By S. A. BARKER, E. J. BOURNE, G. T. BRUCE, W. B. NEELY, and M. STACEY.

[Reprint Order No. 5218.]

A dextran elaborated by *Betacoccus arabinosaceous* (Birmingham strain) is shown to be a branched polyglucosan, in which the principal glucosidic linkages are α-1 : 6, and the branch points involve positions 1 and 3. The average chain length is 6—7 glucose residues.

PREVIOUS workers have established that there is one group of dextrans consisting of long, and virtually unbranched, chains of α-1 : 6-D-glucopyranose units, while a second group is comprised of highly branched dextrans, in which short chains of the above type are joined by 1 : 4-branches [see the review by Stacey and Ricketts (*Fortschr. Chem. Org. Naturstoffe*, 1951, **8**, 28)]. As we have previously reported briefly (Stacey, I.U.P.A.C. Congr., New York, Sept., 1951; Barker, Bourne, Bruce, and Stacey, *Chem. and Ind.*, 1952, 1156), yet a third type of dextran has been discovered in which 1 : 3-glucosidic linkages constitute the branch points. A detailed account of structural studies on this dextran is now presented.

The dextran, elaborated by *Betacoccus arabinosaceous* (Birmingham strain), was isolated from a sucrose medium in which the potassium chloride, *p*-aminobenzoic acid, peptone, and ferrous sulphate, used by Stacey and Swift (*J.*, 1948, 1555), were replaced by a yeast extract. A purified sample of the dextran had $[\alpha]_D^{21}$ +202° in N-sodium hydroxide; it was virtually free from minerals, nitrogenous impurities, and lower saccharides. Paper-chromatographic analysis of a hydrolysate showed glucose (later crystallised), and traces of two other components, which were possibly fructose and hydroxymethylfurfuraldehyde.

* Part I, *J.*, 1954, 1925.

No structural significance is necessarily attached to the detection of this ketose, which may have arisen from an impurity of levan (levans are known to be synthesised by certain dextran-producing organisms), or may have resulted from epimerisation of glucose. The extent of the conversion of the dextran into glucose was shown by cuprimetric titration to be 96%.

The dextran was methylated with sodium and methyl iodide in liquid ammonia at −55°, by a modification of the methods employed by Freudenberg and Boppel (*Ber.*, 1938, **71**, 2505) and Hodge, Karjala, and Hilbert (*J. Amer. Chem. Soc.*, 1951, **73**, 3312). The product (62% yield) had OMe 43·3% (a tri-*O*-methylglucosan requires OMe, 45·6%), ash 0·5%, and $[\alpha]_D^{21}$ +214° (in $CHCl_3$). A paper chromatogram of a hydrolysate of the trimethyl ether revealed two components, having R_F values and staining properties identical with those of 2 : 3 : 4 : 6-tetra- and 2 : 3 : 4-tri-*O*-methylglucose, together with a third component (R_G 0·64, red stain), which was neither 2 : 3-di-*O*-methylglucose (R_G 0·69, brown stain) nor 3 : 4-di-*O*-methylglucose (R_G 0·65, brown stain). This third component (M_G 0·05) could again be differentiated from 2 : 3-di-*O*-methylglucose (M_G 0·12) and 3 : 4-di-*O*-methylglucose (M_G 0·31) by ionophoresis in borate buffer (Foster, *Chem. and Ind.*, 1952, 828); its very low M_G value made it virtually certain that it was the 2 : 4-derivative (cf. Foster, *J.*, 1953, 982), a conclusion which was confirmed subsequently when it was shown that it could not be distinguished, by chromatography or ionophoresis, from a sample of 2 : 4-di-*O*-methylglucose kindly supplied by Drs. D. J. Bell and D. J. Manners. A quantitative assay on filter paper, essentially as described by Hirst, Hough, and Jones (*J.*, 1949, 928), showed that the hydrolysate of the tri-*O*-methyldextran contained (as molecular proportions): 2 : 4-di-*O*-methylglucose, 26; 2 : 3 : 4-tri-*O*-methylglucose, 57; 2 : 3 : 4 : 6-tetra-*O*-methylglucose, 17. This proportion of the tetramethyl ether corresponded to an average chain length of *ca.* 6 glucose units.

Confirmation of the identity of the methylglucoses was obtained on larger-scale fractionation of the hydrolysate on a silica gel column (Bell, *J.*, 1944, 473). The 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose was characterised as the crystalline α-anomer and as the aniline derivative; the trimethyl ether by conversion into *N*-phenyl-2 : 3 : 4-tri-*O*-methyl-D-glucosylamine; and the 2 : 4-di-*O*-methyl-D-glucose by crystallisation from ethyl acetate and as the aniline derivative.

The mixture of saccharides produced by partial hydrolysis of the dextran was fractionated on a charcoal column (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677). *iso*Maltose, identified as its crystalline β-octa-acetate, constituted the major portion (at least 90%) of the disaccharide fraction. It was accompanied by a second disaccharide, which behaved similarly to nigerose and laminaribiose, but differently from maltose, when submitted to paper chromatography either as the free sugar or as its benzylamine derivative (Bayly and Bourne, *Nature*, 1953, **171**, 385). Yet again, the *iso*maltotriose, which formed the bulk of the trisaccharide fraction, was accompanied by another trisaccharide having an R_F value consistent with the presence of a 1 : 6- and a 1 : 3-linkage (Bayly and Bourne, *loc. cit.*).

The dextran consumed 1·67 mol. of periodate, and produced 0·74 mol. of formic acid, per anhydroglucose unit, when oxidised for 93 hr. at 29°. On the assumption that only 1 : 3-branches were present, the former figure indicated a chain length of 6 glucose residues (in good agreement with the methylation evidence), while the latter corresponded to a chain length of only 4 units. This low conversion into formic acid (0·74 mol. instead of 0·83 mol.) may well be attributable to the known inaccuracy of the determination in the presence of oxidised polysaccharides, and possibly also to traces of levan and protein. Hydrolysis of the periodate-oxidised dextran gave, *inter alia*, a component with an R_F value equal to that of glucose, again in conformity with the presence of 1 : 3-branch links. The proportion of glucose in the mixture corresponded to a chain-length of *ca.* 7 units.

Finally, the infra-red absorption spectrum of the dextran was consistent with the structure now assigned (cf. Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171). There were absorption peaks at 917 and 768 $cm.^{-1}$ (α-1 : 6-linkages), at 794 $cm.^{-1}$ (α-1 : 3-linkages), and at 841 $cm.^{-1}$ (this band is shown by α-, but not β-, anomers in the D-glucopyranose series).

Thus, we reach our conclusion that the branch points of the dextran entail principally 1 : 3-linkages from four independent observations, based on methylation, partial hydrolysis to oligosaccharides, oxidation with periodate, and infra-red analysis. It should be noted that the strain of *Betacoccus arabinosaceous* used for the production of the dextran was derived, through many sub-cultures, over a period of about five years, from that isolated by Stacey and Swift (*loc. cit.*) which was claimed to elaborate a dextran with the more usual 1 : 4-branches. It is, of course, possible that a mutation, or a strain selection, had occurred during the interval; alternatively, it may be that the earlier authors were misled by the fact that the aniline derivative of their di-*O*-methyl-D-glucose was somewhat impure, and that its melting point was unfortunately close to that of *N*-phenyl-2 : 3-di-*O*-methyl-D-glucosylamine.

During the course of this investigation, other workers have reported the behaviour of dextrans during periodate oxidations, and have concluded that periodate-resistant units (probably linked through position 3) are present in certain types (cf. Lohmar, *J. Amer. Chem. Soc.*, 1952, **74**, 4974; Abdel-Akher, Hamilton, Montgomery, and Smith, *ibid.*, p. 4970; Jeanes and Wilham, *ibid.*, p. 5339). In addition, it has been shown that some dextrans contain more than one component, which situation is perhaps analogous to the case of starch (Burket and Melvin, *Science*, 1952, **115**, 516; Lohmar, *loc. cit.*; Jeanes and Wilham, *loc. cit.*).

Experimental

Purification of the Crude Dextran.—The dextran (kindly supplied by Dextran Ltd.) had been isolated by precipitation with excess of acetone from culture media (containing per l. : extract from 200 g. of yeast; $Na_2NH_4PO_4$, 5 g.; KH_2PO_4, 1 g.; $MgSO_4,7H_2O$, 0·5 g.; sucrose, 100 g.) of *Betacoccus arabinosaceous* (Birmingham strain), after incubation for 2—3 days at 25°. The crude polysaccharide (40 g.; moisture, *ca.* 12%) was dispersed by shaking it in water (1350 c.c.) for 15 hr. 0·1M-Phosphate buffer (200 c.c.; pH, 6·8) was added, and the whole diluted with water to 1750 c.c. The dispersion was boiled for 45 min., then cooled, and the insoluble material (0·59 g.) collected in a Sharples supercentrifuge. Protein was removed from the concentrated solution (800 c.c.) by the method of Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425), involving three partitions with equal volumes of chloroform–amyl alcohol (3·5 : 1). The polysaccharide was precipitated from the aqueous solution (concentrated to 750 c.c.) with ethanol (3 l.). After three such precipitations, it was dissolved in water (400 c.c.), containing toluene and a trace of sodium ethyl mercurithiosalicylate, and dialysed at 0° for 72 hr., before being freeze-dried. The dextran (23·2 g.) was ground in ether to a powder, and, after being dried *in vacuo* over phosphoric oxide at 60°, had ash, 0·3; N, 0·2%; $[\alpha]_D^{21}$ +202° (*c*, 0·82 in N-sodium hydroxide).

Paper chromatography of the purified dextran, using the upper phase of a mixture of *n*-butanol (40%), ethanol (10%), water (49%), and ammonia (1%) as the solvent, and the usual naphtharesorcinol, aniline hydrogen phthalate, and ammoniacal silver nitrate sprays, failed to reveal any oligosaccharides.

Acidic Hydrolysis of the Purified Dextran.—The polysaccharide (20 mg.) was hydrolysed with 1·4N-sulphuric acid (1·4 c.c.) at 100° for 5 hr. in a sealed tube. After removal of ions by the method of Consden, Gordon, and Martin (*Biochem. J.*, 1947, **41**, 590), the neutral hydrolysate was examined by paper chromatography, as described above; the main component had an R_g value equal to that of glucose; traces of compounds which were probably fructose (*ca.* 0·1—0·2%) and hydroxymethylfurfuraldehyde were also detected.

Another sample of the polysaccharide was hydrolysed for 5 hr. with 1·5N-sulphuric acid at 100°, and the glucose produced was determined by cuprimetric titration (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687). After a small correction (2%) for the loss in reducing power which occurs when glucose itself is treated with acid under these conditions (Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224), the extent of the conversion corresponded to 96%.

After hydrolysis of another sample (0·156 g.) of the dextran, during which $[\alpha]_D$ fell from +201° to +52° (constant), α-D-glucose (30%) was obtained, having m. p. and mixed m. p. 143—145°, $[\alpha]_D^{15}$ +110° (3 min.) ⟶ +53·7° (17 hr., equil.) (*c*, 0·40 in H_2O).

Methylation of the Purified Dextran.—The dextran (10·52 g.) was treated with sodium and methyl iodide in dry redistilled liquid ammonia at −55°, a modification of the methods employed by Freudenberg and Boppel (*loc. cit.*) and Hodge, Karjala, and Hilbert (*loc. cit.*) being used. After four additions of the methylating reagents (reaction times : sodium, 2 hr.;

methyl iodide, 1 hr.) had been made, the ammonia was allowed to evaporate, with exclusion of moisture, the last traces being removed at 75°/20 mm. After dialysis, the freeze-dried product (10·53 g.) had OMe, 28·7%. Repetition of the methylation procedure gave a product (9·83 g.) having OMe, 42·7%. The crude methyl ether obtained after a final remethylation (9·08 g.; ash, 1·1%) was purified by removal of grease in a Soxhlet apparatus by light petroleum (b. p. 60—80°), and subsequent extraction of the residual material with dry chloroform. The cloudy extract was centrifuged, the supernatant liquid evaporated, and the residue ground with ether. The methylated dextran (8·17 g.) showed $[\alpha]_D^{21}$ +214° (*c*, 0·24 in $CHCl_3$) (Found: OMe, 43·3; ash, 0·5. Calc. for $C_9H_{16}O_5$: OMe, 45·6%).

Identification of the Methyl Sugars obtained from the Methylated Dextran.—The polysaccharide ether (0·054 g.), in dry chloroform (1 c.c.), was treated with 8% methanolic hydrogen chloride (1 c.c.) in a sealed tube at 100° for 8 hr., and then, after removal of the solvent, with 4% hydrochloric acid (5·5 c.c.) at 100° for 6 hr., the optical rotation then being constant. The resulting solution of methylglucoses was freed from ions, and concentrated to a syrup (0·056 g.). A paper chromatogram of the hydrolysate, irrigated for 24 hr. in the manner previously described, showed three components after being sprayed with aniline hydrogen phthalate (Partridge, *Nature*, 1949, **164**, 443). Two of the components had R_F values and staining properties identical with those of 2 : 3 : 4-tri-*O*-methylglucose and 2 : 3 : 4 : 6-tetra-*O*-methylglucose. The third component (R_G 0·64, red stain) could be differentiated on the same chromatogram from 2 : 3- (R_G 0·69, brown stain) and 3 : 4-di-*O*-methylglucose (R_G 0·65, brown stain), but not from 2 : 4-di-*O*-methylglucose. The same component, after isolation from a paper chromatogram, was submitted to ionophoresis in borate buffer (pH, 10) (Foster, *loc. cit.*); its M_G value and staining reactions were identical with those of 2 : 4-di-*O*-methylglucose (M_G 0·05) isolated from a hydrolysate of methyl 2 : 4-di-*O*-methyl-β-D-glucopyranoside, produced from the methyl ether of tritylated laminarin. 2 : 3-Di-*O*-methylglucose had M_G 0·12, while 3 : 4-di-*O*-methylglucose had M_G 0·31.

Determination of the Methyl Sugars obtained from the Methylated Dextran.—The remainder of the hydrolysate mentioned above was analysed by a method which was essentially that used by Hirst, Hough, and Jones (*loc. cit.*), with minor modifications introduced by Barker, Bourne, and Wilkinson (*J.*, 1950, 3027). As a result of several independent quantitative determinations, based on oxidation with hypoiodite, the calculated composition of the mixture was as given on p. 2396.

Isolation of the Methyl Sugars obtained from the Methylated Dextran.—The methylated dextran (3·00 g.), after methanolysis and hydrolysis, gave a syrup (3·05 g.), which was freed from ions, and then fractionated by Bell's method (*loc. cit.*) on a column of silica gel (Gordon, Martin, and Synge, *Biochem. J.*, 1943, **37**, 79). Three fractions (I, 0·537 g.; II, 1·950 g.; III, 0·379 g.) were obtained; paper-chromatographic analysis and ionophoresis showed them to contain, respectively, 2 : 3 : 4 : 6-tetra-, 2 : 3 : 4-tri-, and 2 : 4-di-*O*-methylglucose.

Fraction I (0·396 g.), crystallised from ether, gave 2 : 3 : 4 : 6-tetra-*O*-methyl-α-D-glucose (0·088 g.), m. p. and mixed m. p. 82—84°, $[\alpha]_D^{15}$ +95·3° (4 min.) ⟶ +83·0° (17 hr., equil.) (*c*, 0·40 in H_2O) (Found: C, 50·7; H, 8·5; OMe, 51·8. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5; OMe, 52·5%). The syrup obtained by concentration of the mother-liquors, treated with aniline (0·30 c.c.) in ethanol (10 c.c.) under reflux for 2 hr., gave *N*-phenyl-2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucosylamine (0·040 g.), m. p. 135—136° (cf. Peat, Schlüchterer, and Stacey, *J.*, 1939, 581).

Fraction II (0·100 g.), refluxed with aniline (0·60 c.c.) in ethanol (1·00 c.c.) for 4 hr., gave crystals (0·030 g.), m. p. 132°, raised by two recrystallisations from ether–light petroleum (b. p. 40—60°) to 147—148°, not depressed in admixture with *N*-phenyl-2 : 3 : 4-tri-*O*-methyl-D-glucosylamine. Peat, Schlüchterer, and Stacey (*loc. cit.*) gave m. p. 145—146°.

Fraction III (0·065 g.), crystallised from dry ethyl acetate, gave a small yield of a product, m. p. 125—128°, not depressed in admixture with 2 : 4-di-*O*-methyl-β-D-glucose. The syrup recovered from the mother-liquors was kept in aniline (0·40 c.c.)–ethanol (0·50 c.c.) at 20° for 48 hr., and the crystalline precipitate (0·029 g.) was recrystallised from ether–light petroleum (b. p. 40—60°). The product had m. p. 197—199°, alone and in admixture with *N*-phenyl-2 : 4-di-*O*-methyl-D-glucosylamine, but depressed to 137—140° by the isomeric 3 : 4-dimethyl ether, both samples being supplied by Dr. Bell (Found: C, 59·1; H, 7·2; N, 4·6. Calc. for $C_{14}H_{21}O_5N$: C, 59·3; H, 7·5; N, 4·9%).

Partial Hydrolysis of the Purified Dextran.—The dextran (2·46 g.) was partially hydrolysed with N-sulphuric acid (100 c.c.) at 85° for 5·5 hr., $[\alpha]_D^{19}$ having then fallen to +133°. The acidic solution of saccharides was fractionated on a charcoal column (Whistler and Durso, *loc. cit.*),

which was washed as shown in the Table. Each eluate was neutralised with barium carbonate (when necessary), filtered, and concentrated to a syrup, and the saccharides were extracted with hot methanol (A—D), or hot 50% aqueous methanol (E—I). Thereafter, they were obtained as freeze-dried powders, and analysed by paper chromatography.

Partial acidic hydrolysis of the dextran.

Eluant	Fraction	Wt. (g.) of product	Probable sugar components (by paper chromatography)
Water, 300 c.c.	A	0·802	Glucose, fructose (<5%)
5% Ethanol (1), 200 c.c.	B	0·234	*iso*Maltose
5% Ethanol (2), 100 c.c.	C	0·017	*iso*Maltose, nigerose, trisaccharide
5% Ethanol (3), 400 c.c.	D	0·187	Trisaccharides
10% Ethanol (1), 100 c.c.	E	0·003	Trisaccharides
10% Ethanol (2), 200 c.c.	F	0·175	Tetrasaccharide
10% Ethanol (3), 100 c.c.	G	0·045	Tetrasaccharide, pentasaccharide
10% Ethanol (4), 400 c.c.	H	0·141	Higher saccharides
35% Ethanol, 400 c.c.	I	0·915	Higher saccharides

Part (0·310 g.) of fraction A was further characterised by conversion into penta-*O*-acetyl-β-D-glucopyranose (0·237 g.), m. p. and mixed m. p. 128—129°. Fraction B had $[\alpha]_D^{19}$ +119° (equil.) (*c*, 0·43 in H_2O); ash, 1·1%. Montgomery, Weakley, and Hilbert (*J. Amer. Chem. Soc.*, 1949, **71**, 1682) report $[\alpha]_D^{25}$ +120° (equil.) (*c*, 1·2 in H_2O) for *iso*maltose. A portion (0·075g .) of this product, treated with acetic anhydride (0·75 c.c.) and fused sodium acetate (0·02 g.) at 100—110° for 1 hr., gave β-*iso*maltose octa-acetate (0·090 g.), m. p. and mixed m. p. 144—145°, $[\alpha]_D^{20}$ +99·6° (*c*, 0·38 in $CHCl_3$) (Found: C, 49·7; H, 5·5. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%). Fraction C contained an additional disaccharide, which, when submitted to paper chromatography, either as the free sugar or as its benzylamine derivative (Bayly and Bourne, *loc. cit.*), was indistinguishable from nigerose and laminaribiose. Fraction D had the same R_F value as *iso*maltotriose, and, after partial hydrolysis with N-sulphuric acid at 90° for 0·5, 1·0, and 2·0 hr., *iso*maltotriose, *iso*maltose, and glucose were identified by paper chromatography.

Periodate Oxidation of the Purified Dextran.—The procedure adopted was essentially that of Jeanes and Wilham (*J. Amer. Chem. Soc.*, 1950, **72**, 2655), which incorporates Fleury and Lange's method (*J. Pharm. Chim.*, 1933, **17**, 107, 196) for the determination of the quantity of periodate consumed, and that of Halsall, Hirst, and Jones (*J.*, 1947, 1427), with certain modifications, for the determination of the quantity of formic acid produced. The number of moles of sodium periodate consumed per unit of anhydroglucose was: 44 hr., 1·58; 74 hr., 1·65; 93·5 hr., 1·67; and the corresponding figures for formic acid produced were: 0·73, 0·75, 0·74.

Ethylene glycol was added to destroy the excess of periodate, and sodium hydroxide to neutralise the formic acid in a solution of dextran (0·0615 g.), which had been submitted to periodate oxidation for 128 hr., under the same conditions. The oxidised polysaccharide (0·047 g.) was obtained by removal of ions from this solution and concentration under reduced pressure. After hydrolysis with 1·4N-sulphuric acid (5 c.c.) at 100° for 9 hr., the solution was neutralised with barium carbonate, filtered, and concentrated. The syrup (0·048 g.) obtained was dissolved in water (2 c.c.), and a drop of the solution was examined on a paper chromatogram, which, when developed with aniline hydrogen phthalate, showed a component having an R_F value equal to that of glucose, together with a red-staining faster-moving component of unknown identity. The amount of glucose present in the solution was determined by incorporation of a known amount (0·005 g.) of tetra-*O*-methylglucose in a portion (1 c.c.) of the hydrolysate, followed by determination of the molar proportions of the two sugars, after separation by paper chromatography, by the method of Hirst, Hough, and Jones (*loc. cit.*). In this way, it was calculated that 9·8 mg. of glucose had been obtained from 61·5 mg. of dextran, indicating that one glucose unit in every seven of the dextran was linked through position 3.

The authors are indebted to Dextran Ltd. for financial assistance, and for the sample of dextran studied; to Drs. D. J. Bell and D. J. Manners for gifts of di-*O*-methylglucose samples; and to the British Rayon Research Association and Courtaulds' Scientific and Educational Trust Fund for financial assistance to two of them (S. A. B. and G. T. B.).

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, March 19th*, 1954.]

The Chemistry of Hop Constituents. Part VI. The Structure of Cohumulone.*

By G. A. Howard and A. R. Tatchell.

[Reprint Order No. 5197.]

Cohumulone, $C_{20}H_{28}O_5$, closely resembles humulone. Thus, hydrogenolysis of cohumulone leads to cohumuloquinol and, thence, oxidation *via* the quinone affords *iso*cohumulinic acid. Similarly alkaline hydrolysis of cohumulone gives cohumulinic acid, $C_{14}H_{20}O_4$, which contains an *iso*butyryl and a 3-methylbut-2-enyl side-chain and is thus a lower homologue of humulinic acid. Cohumulone and humulone therefore differ structurally only in that they include respectively an *iso*butyryl and an *iso*valeryl side-chain.

A PRELIMINARY account of the properties of cohumulone which occurs together with humulone in many varieties of hops (Howard and Tatchell, *J. Inst. Brew.*, 1953, 491) has already been given (Howard and Tatchell, *Chem. and Ind.*, 1953, 436) and the present paper amplifies these earlier reports. Cohumulone, which has been obtained only as an oil, behaves as a single component on counter-current distribution in *iso*octane–phosphate buffer at pH 8·0 or in *iso*octane–phosphate buffer at pH 7·2 containing 15% of methanol. Its lead salt has a composition consistent with the formulation $C_{20}H_{26}O_5Pb$ from which the formula $C_{20}H_{28}O_5$ may be inferred for cohumulone itself, as compared with $C_{21}H_{30}O_5$ for humulone. This result agrees both with the equivalent of 351 found experimentally and with the results of Rigby and Bethune (*J. Amer. Chem. Soc.*, 1952, **74**, 6118). Cohumulone thus appears formally to be a lower homologue of humulone. The infra-red absorption spectra of the two compounds are similar as are also their ultra-violet spectra (Harris, Howard, and Pollock, *J.*, 1952, 1906; Howard and Tatchell, *loc. cit.*) and this circumstance, together with the close chemical similarities between the two compounds, suggests that they contain similar functional groups similarly arranged.

Hydrolysis of cohumulone by boiling N-alkali gave results which present an interesting comparison with those obtained with humulone (cf. Harris, Howard, and Pollock, *loc. cit.*), in both cases *iso*butyraldehyde and 4-methylpent-3-enoic acid being obtained. The hydrolysate of cohumulone contained however a new compound, cohumulinic acid, m. p. 79—80°, corresponding to the humulinic acid, m. p. 92°, obtained from humulone. Cohumulinic acid, $C_{14}H_{20}O_4$, has one methylene group less than humulinic acid (Harris, Howard, and Pollock, *loc. cit.*). It was readily hydrogenated catalytically to dihydrocohumulinic acid, $C_{14}H_{22}O_4$. Ozonolysis confirmed the presence of a double bond, acetone being obtained as the sole volatile carbonyl product.

The ultra-violet and infra-red spectra and the general reactions of cohumulinic acid are respectively so similar to those of humulinic acid as to indicate that they contain the same central nucleus and functional groups and differ only in their side-chains. When dihydrocohumulinic acid was oxidised by alkaline hypobromite, *iso*butyric acid was obtained in good yield. Dihydrocohumulinic acid and thus presumably cohumulinic acid and cohumulone therefore contain an *iso*butyryl side-chain in place of the *iso*valeryl group in humulone and its derivatives.

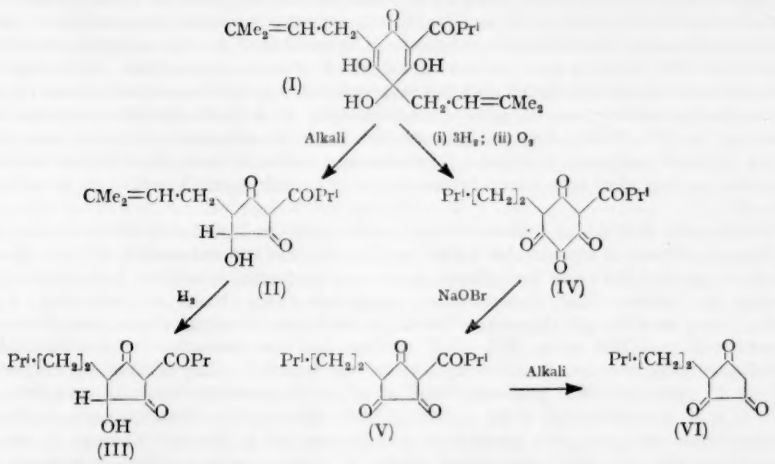
The nature of the alkyl side-chain of cohumulinic acid remained to be determined. Oxidation of dihydrocohumulinic acid with periodate gave an oil which was hydrolysed by alkali to 3-methylbutan-2-one, 6-methylheptan-2-one, and *iso*butyric acid. This further indicates the close similarity of dihydrohumulinic and dihydrocohumulinic acids and confirms the presence in the latter of both an *iso*butyryl and a 3-methylbutyl group. This, together with the formation of acetone during the ozonolysis of cohumulinic acid, implies that the latter contains the same 3-methylbut-2-enyl side-chain as humulinic acid (cf. Harris, Howard, and Pollock, *loc. cit.*). Cohumulinic acid must consequently be (II), its dihydro-derivative (III), and cohumulone itself (I).

* Part V, *J. Inst. Brewing*, 1953, 480.

On two occasions the attempted hydrogenation of cohumulinic acid gave, instead of the usual dihydrocohumulinic acid, a new acidic compound, $C_{14}H_{24}O_3$, m. p. 162—163° (cf. Howard and Tatchell, *loc. cit.*). This material has only one ultra-violet absorption band, whereas humulinic and cohumulinic acid and their dihydro-derivatives have the two bands usually exhibited by compounds containing the triketomethine grouping. The spectrum of the compound $C_{14}H_{24}O_3$ is, however, similar to that of 4-hydroxy-2-methyl-*cyclo*pentane-1 : 3-dione (Orchin and Butz, *J. Amer. Chem. Soc.*, 1943, **65**, 2296) and of 2-ethyl-4-*n*-propyl*cyclo*pentane-1 : 3-dione (Woodward and Blout, *ibid.*, p. 562). The available evidence is thus consistent with the formulation of this material as 4-hydroxy-5-3′-methylbutyl*cyclo*pentane-1 : 3-dione and this is supported by the fact that the compound rapidly reduces one molar equivalent of periodate. Investigations are in progress to elucidate the conditions under which this compound is produced and to establish its structure.

Cohumulone consumes three molar equivalents of hydrogen when hydrogenated in methanolic palladous chloride. The colourless solution so obtained absorbed one equivalent of oxygen to give a solution from which the purple crystalline cohumuloquinone, $C_{15}H_{20}O_5$ (IV), was isolated and characterised as its azine with *o*-phenylenediamine. Hypobromite oxidation of the quinone led to an *iso*cohumulinic acid, $C_{14}H_{20}O_4$ (V), which is hydrolysed by alkali to 3-3′-methylbutyl*cyclo*pentane-1 : 2 : 4-trione (VI) which is obtained by a similar degradation of humulone (Harris, Howard, and Pollock, *loc. cit.*).

The conclusion to be drawn from these investigations is that cohumulone differs from humulone only in containing an *iso*butyryl in place of the *iso*valeryl group.



The results obtained by ozonolysis of cohumulone, however, appeared at one time to be inconsistent with the above conclusion. Oxidation of humulone by ozone has been reported (Carson, *J. Amer. Chem. Soc.*, 1951, **73**, 4652; Riedl, *Brauwiss.*, 1951, 51) to yield acetone as the sole volatile product in a yield indicating the presence of two *iso*propylidene groups in humulone. The volatile fission products resulting from the ozonolysis of cohumulone gave, however, a mixture of 2 : 4-dinitrophenylhydrazones. Various attempts to resolve the mixture having failed recourse was had to reverse-phase partition chromatography with benzene and formamide as the stationary and the mobile phase respectively (Howard and Tatchell, *Chem. and Ind.*, 1954, 219). Under these conditions the mixture was separated into the 2 : 4-dinitrophenylhydrazones of acetaldehyde and acetone, the yield of the latter, however, accounting only for that required by the presence of one *iso*propylidene group. On re-examination of the ozonolysis of humulone it was found that this reaction also gave acetaldehyde and acetone. Detailed study finally revealed that

ozonolysis at −58° in chloroform with the avoidance of prolonged reaction converts both humulone and cohumulone into acetaldehyde and acetone, although under these conditions the yield of the latter in each case was sufficient to indicate the presence of two *iso*propylidene groups. The formation of acetaldehyde remains without explanation.

The similarity between cohumulone and humulone being established as stated above, the main reactions of cohumulone (I) may be summarised as in the formulæ. The easy hydrogenolysis of carbon–carbon bonds observed in the sennoside series (Stoll, Becker, and Helfenstein, *Helv. Chim. Acta*, **1950**, **33**, 313) suggests by analogy that the hydrogenolysis of structures such as (I) is not unreasonable. Such formulations are therefore considered less open to the criticisms made earlier (Harris, Howard, and Pollock, *loc. cit.*).

Experimental

Cohumulone was prepared by the counter-current method (Howard and Tatchell, *loc. cit.*). The solvent system *iso*octane–0·5M-phosphate buffer of pH 8·0 which was used earlier and resulted in the separation of cohumulone and humulone after about 200 transfers was incapable of handling large quantities of material as formation of emulsions led to loss of cohumulone by aerial oxidation. However, the system *iso*octane–0·5M-potassium phosphate buffer of pH 7·2 containing 15% of methanol proved more satisfactory in handling up to 30 g. of humulone–cohumulone mixtures.

Cohumulone had $[\alpha]_D$ −195° in MeOH and an equiv. wt. of 351 (Calc. for $C_{20}H_{28}O_5$, 348). The *lead* salt was prepared in the usual way (Found: C, 43·2; H, 4·9; Pb, 36·7. $C_{20}H_{26}O_5Pb$ requires C, 43·4; H, 4·7; Pb, 37·4%).

Alkaline Hydrolysis of Cohumulone.—(*a*) Cohumulone (720 mg.) in ethanol (10 c.c.) and N-sodium hydroxide (13 c.c.) was boiled under reflux in a stream of nitrogen for 1·5 hr., the effluent gases being passed into aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. The hydrolysate was concentrated to 10 c.c. by distillation, the distillate being collected in 2 : 4-dinitrophenylhydrazine hydrochloride solution. The combined 2 : 4-dinitrophenylhydrazones were extracted with benzene and chromatographed on alumina in benzene. One main band only was observed which was eluted and the material obtained by concentration was recrystallised from methyl*cyclo*hexane, to give *iso*butaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 177—179°. The residual solution from the alkaline hydrolysis was acidified with dilute sulphuric acid and distilled. The acid was extracted from the distillate with ether and converted in the usual way into *p*-bromophenacyl 4-methylpent-3-enoate, m. p. and mixed m. p. 91—92°.

(*b*) Cohumulone (4·6 g.) in ethanol (9 c.c.) and N-sodium hydroxide (63 c.c.) was heated under reflux in a stream of nitrogen for 1·5 hr. and the solution concentrated to 50 c.c. Carbonyl compounds in the distillate and the effluent gases were converted into their 2 : 4-dinitrophenylhydrazones as before. The latter were extracted with benzene, and the solution chromatographed on silica gel (Merck). The main band gave material which, after recrystallisation from methanol, had m. p. 182—183° undepressed on admixture with *iso*butaldehyde 2 : 4-dinitrophenylhydrazone; no other hydrazone was isolated. The alkaline hydrolysate was acidified at 0° and the resin produced kept at 0° until crystallisation was complete. The *cohumulinic acid* thus obtained (2·95 g., 88%) had, after recrystallisation successively from *cyclo*hexane, from methanol, and again from *cyclo*hexane, m. p. 79—80° (Found: C, 66·5; H, 7·85%; equiv., 248. $C_{14}H_{20}O_4$ requires C, 66·6; H, 7·9%; equiv., 252). It had pK 3·9 in aqueous ethanol. The infra-red absorption spectrum of cohumulinic acid in Nujol mull shows bands (μ) at 3·00 s, 3·89 s, 6·13 s, 6·30 s, 7·00 s, 7·31 m, 7·65 m, 7·82 s, 7·92 s, 8·02 s, 8·53 w, 8·85 w, 9·20 s, 9·75 w, 10·35 m, 10·9 w, and 11·57 w, where s = strong, m = medium, and w = weak. We are indebted to Prof. A. R. Todd and Dr. R. N. Haszeldine for this spectrum which was determined in a Perkin–Elmer double-beam instrument.

(*c*) In a similar experiment cohumulone (6·5 g.) gave a mixture of 2 : 4-dinitrophenylhydrazones (1·7 g.) after chromatography on alumina. A portion (11·3 mg.) of the material was separated on a benzene–formamide partition column (see below), to give *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (5·7 mg. by colorimetric estimation, equiv. to an 18% yield), and acetone 2 : 4-dinitrophenylhydrazone (0·55 mg. by colorimetric estimation, equiv. to a 1·9% yield).

Dihydrocohumulinic Acid.—Cohumulinic acid (2·3 g.), when hydrogenated in methanol (150 c.c.) in the presence of Adams catalyst, absorbed 192 c.c. of hydrogen (calc. for one double bond, 207), to give a solution which after filtration and evaporation gave *dihydrocohumulinic acid*

(1·69 g., 74%), m. p. 85—87°. Recrystallisation from methanol gave prismatic needles, m. p. 91—92° (Found: C, 66·4; H, 8·8. $C_{14}H_{22}O_4$ requires C, 66·2; H, 8·7%).

Abnormal Hydrogenation of Cohumulinic Acid.—Cohumulinic acid (1·8 g.) was hydrogenated in methanol (150 c.c.) in presence of Adams platinum catalyst; 194 c.c. of hydrogen were absorbed (calc. for one double bond 170 c.c.). The solution gave a *product* as prisms, m. p. 162—163° (795 mg., 46%) after crystallisation from methanol (Found: C, 70·0; H, 10·1%; equiv., 225. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·0%; equiv., 240). Ultra-violet absorption: in acidic ethanol, max. at 250 mμ (ε 13,700); in alkaline ethanol, max. at 275 mμ (ε 21,000). The material had p*K* 6·0 in aqueous ethanol, and was insoluble in chloroform, water, and aqueous sodium hydrogen carbonate but soluble in aqueous sodium hydroxide and methanol. Ferric chloride in methanol gave a weak purple colour fading to brown. The material reduced alkaline permanganate and decolorised bromine in chloroform, but was unaffected by Fehling's solution or ammoniacal silver nitrate. It was recovered unchanged after 1·5 hours' boiling with N-sodium hydroxide and from attempts to prepare an oxime or semicarbazone. It consumed 1·01 molar equivalents of periodate in 3·5 hr., giving crystalline material (purple ferric chloride colour, acid to litmus, slowly gave positive Schiff test) which was hydrolysed by boiling alkali to a mixture of acids and ketones from which *iso*butyric was apparently absent (paper chromatography).

Oxidation of Dihydrocohumulinic Acid by Hypobromite.—To an ice-cooled solution of dihydrocohumulinic acid (1·67 g.) in N-sodium hydroxide solution (67 c.c.) a saturated solution of bromine (3·1 mols.) in water (103 c.c.) was added dropwise during cooling and stirring. A slight excess of bromine was reduced by sodium pyrosulphite, and the solution extracted exhaustively with ether. The extract was washed with water, dried, and evaporated, to give bromoform (995 mg., 60%), b. p. 144—145°. The alkaline oxidation solution was acidified at 0° with dilute sulphuric acid and then extracted exhaustively with ether. The extracted material was distilled at 28 cm., *iso*butyric acid (350 mg., 60%) being collected [*p*-bromophenacyl ester, m. p. and mixed m. p. 72—74°; anilide, m. p. and mixed m. p. 100—101°; R_F 0·57 on Whatman No. 1 paper in *n*-butanol–water–diethylamine (100 : 15 : 1) identical with the R_F value of *iso*butyric acid in this solvent].

Ozonolysis of Humulone.—Humulone (196 mg.) in alcohol-free chloroform was treated with ozonised oxygen for 22 min. To the solution was added powdered zinc (2 g.) and water (30 c.c.), and the mixture was kept for 30 min. and filtered. The residue was washed with water, and the combined filtrate and washings were distilled to low bulk, the distillate being collected in a solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The hydrazones were extracted with benzene, and the extract washed with water, dried (Na_2SO_4), and concentrated. The concentrate was passed over an alumina column (Merck) in dry benzene and the coloured eluate of a single band evaporated. The residue (272 mg.) was dissolved in benzene (50 c.c.), and an aliquot part (25 c.c.) evaporated to give material which when recrystallised from ethanol had m. p. 118—120°. A further aliquot part (4 c.c.) part after evaporation to dryness was chromatographed in formamide (1 c.c.) on a "Silane"-treated kieselguhr column (42 × 1·5 cm.; 20 g. of kieselguhr, 10 ml. of benzene; cf. Howard and Tatchell, *loc. cit.*), with benzene as the stationary and formamide as the mobile phase. Two bands were eluted, each eluant solution was made up to a standard volume with formamide, and the light transmittance determined on a Spekker photoelectric absorptiometer (Ilford Filter No. 602). After extraction of the formamide solutions with benzene, washing of the benzene extract with water, drying, and evaporation, the residues were recrystallised from ethanol. In this manner the first band was identified as acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 158—160°, and the second as acetone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 124°. The preparation of standard curves of acetone and acetaldehyde 2 : 4-dinitrophenylhydrazones in formamide with the Spekker photoelectric absorptiometer enabled the amounts of these compounds in the eluant solutions to be determined; it was calculated that the mixture (21·3 mg.) contained acetaldehyde 2 : 4-dinitrophenylhydrazone (2 mg., 20·6%) and acetone 2 : 4-dinitrophenylhydrazone (14 mg., 128%).

In another experiment humulone (204 mg.) was ozonised in glacial acetic acid (20 c.c.) for 22 min. and worked up as above to give a mixture of 2 : 4-dinitrophenylhydrazones (260 mg.). Separation of this mixture (21 mg.) on the partition column gave acetaldehyde 2 : 4-dinitrophenylhydrazone (3·1 mg., 30·2%) and acetone 2 : 4-dinitrophenylhydrazone (13·5 mg., 127%).

In a further experiment humulone (252 mg.) was ozonised in alcohol-free chloroform (20 c.c.) at −58° until the solution gave no colour with tetranitromethane as external indicator (23 min.). After the addition of zinc (2 g.) and water (30 c.c.) the solution was kept for 1 hr. and then

filtered. Subsequent working up gave a mixture of 2 : 4-dinitrophenylhydrazones (335 mg.), separation of which (33·5 mg.) on the partition column gave acetaldehyde 2 : 4-dinitrophenylhydrazone (4·5 mg., 28%) and acetone 2 : 4-dinitrophenylhydrazone (21·5 mg., 130%).

Ozonolysis of Cohumulone.—Cohumulone (290 mg.) in alcohol-free chloroform (20 c.c.) at −58° was treated with ozonised oxygen until the solution gave no colour with tetranitromethane used as an external indicator (23 min.). After the addition of zinc (2 g.) and water (30 c.c.) the solution was kept for 3 hr., filtered, and distilled, the distillate being collected in a solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. After subsequent treatment as described for humulone a mixture of 2 : 4-dinitrophenylhydrazones (278 mg.) was obtained. The mixture was dissolved in benzene (50 c.c.), an aliquot part (5 c.c.) evaporated to dryness, and the residue (27·8 mg.) separated on the partition column into acetaldehyde 2 : 4-dinitrophenylhydrazone (1·75 mg., 9·4%), m. p. and mixed m. p. 160—162°, and acetone 2 : 4-dinitrophenylhydrazone (20·5 mg. 108%), m. p. and mixed m. p. 124°.

In a second experiment cohumulone (288 mg.) in alcohol-free chloroform was treated with ozonised oxygen at −58° for 33 min. (no colouration of tetranitromethane). After addition of zinc (2 g.) and water (30 c.c.) the solution was kept for 1 hr., then worked up in the usual way. The mixed 2 : 4-dinitrophenylhydrazones (350 mg.) thus obtained were dissolved in benzene (50 c.c.), and an aliquot part (4 c.c.) was evaporated to give a residue (28 mg.) which was dissolved in formamide and chromatographed on the partition column. The two bands on elution yielded acetaldehyde 2 : 4-dinitrophenylhydrazone (2·8 mg., 18·8%) and acetone 2 : 4-dinitrophenylhydrazone (20·6 mg., 132%).

Ozonolysis of Humulinic Acid.—Ozonised oxygen was passed for 15 min. into a solution of humulinic acid (141 mg.) in acetic acid (20 c.c.). The solution was treated with zinc and water as usual and distilled, the distillate being collected in aqueous-ethanolic 2 : 4-dinitrophenylhydrazine hydrochloride. The hydrazones were extracted with benzene, and the extracts washed with water, dried (Na_2SO_4), and concentrated. The concentrate was passed over an alumina column (Merck) in dry benzene and the coloured eluate of a single band evaporated to give acetone 2 : 4-dinitrophenylhydrazone (109 mg., 86%), having m. p. and mixed m. p. 119—121° after recrystallisation from ethanol.

Ozonolysis of Cohumulinic Acid.—Cohumulinic acid (136 mg.) in acetic acid (20 c.c.) was treated with ozonised oxygen for 15 min. The solution was treated as described for humulinic acid, the single 2 : 4-dinitrophenylhydrazone band from the alumina column giving 114 mg. (89%) of acetone 2 : 4-dinitrophenylhydrazone, m. p. 117°, which had m. p. 119—121° when mixed with an authentic specimen.

Oxidation of Dihydrocohumulinic Acid with Periodate.—To dihydrocohumulinic acid (106 mg.) in ethanol (50 c.c.) was added potassium metaperiodate (117 mg., 1·22 equivs.) in water (50 c.c.). After 2 hr. 1·08 equivs. of periodate had been consumed. The solution was acidified and extracted with ether, giving an oily extract which was refluxed for 2 hr. with 2N-sodium hydroxide (30 c.c.). The hydrolysate was steam-distilled, the distillate being collected in methanolic 2 : 4-dinitrophenylhydrazine hydrochloride. The distillation residue was extracted with ether, the extracted material added to the 2 : 4-dinitrophenylhydrazine solution, and the aqueous alkaline residue reserved for later examination.

The 2 : 4-dinitrophenylhydrazones were extracted with benzene, the extracted material was passed down an alumina column (Merck), and the single main band collected. The material from this band (105 mg.) was separated on a benzene-formamide partition column into 3-methylbutane-2-one 2 : 4-dinitrophenylhydrazone (22 mg., 20%), micro-m. p. 120—122°, and 6-methylheptane-2-one 2 : 4-dinitrophenylhydrazone (43·6 mg., 34%), micro-m. p. 82—83°, each undepressed on admixture with authentic material.

The alkaline residue above was acidified and extracted with ether, and the extract washed free from inorganic acid, dried, and evaporated. Paper-chromatographic examination of the residual acids in *n*-butanol–water–diethylamine (100 : 15 : 1) gave three main acid spots, with R_F values 0·5, 0·76, and 0·89 respectively; *iso*butyric acid has R_F 0·5 in this system. Examination with the solvent system *n*-butanol–water–diethylamine (25 : 25 : 1) gave four spots with R_F values 0·23, 0·48, 0·84, and 0·95 respectively.

Cohumuloquinone.—A solution of cohumulone (750 mg.) in methanol (20 c.c.) was shaken for 10 min. with 5 g. of Raney nickel to remove hydrogen sulphide remaining from the decomposition of cohumulone lead salt. The nickel was filtered off and washed with methanol (3 × 20 c.c.), a solution (5% w/v) of palladous chloride in methanol (0·2 c.c.) added to the combined filtrate and washings, and the solution hydrogenated. Uptake ceased when 134 c.c. of hydrogen had been absorbed (calc. for $3H_2$, 144 c.c.). The colourless solution was

filtered and the filtrate shaken in air, 39 c.c. of oxygen being absorbed (calc. for O_2, 48 c.c.). The purple solution was evaporated in a vacuum and the residue recrystallised twice from methanol, to give red needles (281 mg., 47%) (Found: C, 61·4; H, 7·8. $C_{15}H_{20}O_3,CH_3{\cdot}OH$ requires C, 61·6; H, 7·7%). The m. p. of the material was 72—73° but, like that of humuloquinone, the m. p. of *cohumuloquinone* was erratic. With *o*-phenylenediamine the quinone formed a purple *azine*, m. p. 129—130°, depressed to 93—100° on admixture with humuloquinone azine of m. p. 110—111° (Found: N, 7·6. $C_{21}H_{24}O_2N_2$ requires N, 7·9%).

iso*Cohumulinic Acid*.—To an ice-cooled solution of cohumuloquinone (280 mg.) in N-sodium hydroxide (4 c.c.) and water (2 c.c.) was added slowly with stirring a saturated solution of bromine in water (15 c.c.). The colourless solution was acidified at 0° with dilute hydrochloric acid. The crystalline *acid* (120 mg.) was recrystallised twice from methanol, giving yellow needles, m. p. 118° (Found: C, 66·8; H, 8·3. $C_{14}H_{20}O_4$ requires C, 66·6; H, 7·9%).

Alkaline Hydrolysis of iso*Cohumulinic Acid*.—A solution of the acid (260 mg.) in freshly prepared 2N-sodium hydroxide (15 c.c.) was refluxed for 20 min. under nitrogen. The cooled solution was filtered to remove brown gum, and the filtrate acidified at 0° with dilute hydrochloric acid. The sticky crystals produced were recrystallised four times from benzene, giving 13 mg. of material, m. p. 102° undepressed on admixture with 3-3′-methylbutyl*cyclo*pentane-1 : 2 : 4-trione. This mixed m. p. is not considered to be proof of the structure of the hydrolysis product.

The authors thank Sir Ian Heilbron, D.S.O., F.R.S., and Dr. A. H. Cook, F.R.S., for their advice and encouragement. They are also grateful to Professor D. H. R. Barton, F.R.S., for helpful discussions.

THE BREWING INDUSTRY RESEARCH FOUNDATION,
NUTFIELD, SURREY.

[*Received, March 11th*, 1954.]

Steric Relations between Ionisation of Aralkyl Chlorides and Dissociation of Anilinium Ions. Part I.

By G. BADDELEY, J. CHADWICK, and H. T. TAYLOR.

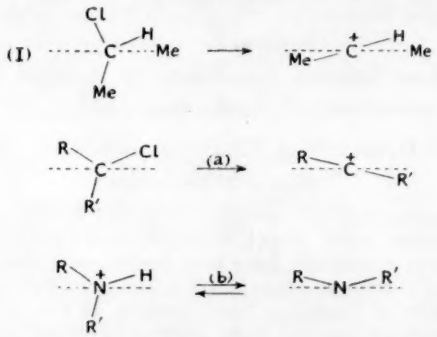
[Reprint Order No. 5024.]

Rates of solvolysis of the chlorides R·CHPhCl in 80% aqueous ethanol, where R is methyl, ethyl, propyl, *iso*propyl, 1-ethylpropyl, *tert.*-butyl, and 1 : 1-dimethylpropyl severally, have been determined. Reactivity decreases in the order R = primary > secondary > tertiary alkyl group and, since this is the order of increasing basic strength of the aniline derivatives R·NHPh, it is argued that this is the order of increasing steric hindrance of ionisation of the chlorides and of dissociation of the corresponding anilinium ions.

A COMPLETE theory of the effect of substituents on (*a*) reaction rate and (*b*) equilibrium incorporates the change of steric interaction effected by the difference in intramolecular spatial configuration between (*a*) reactant and transition state and (*b*) reactant and product. This change, which, whether unimolecular or bimolecular reactions are concerned, is not related to the probability of approach of reactants, was first introduced to account for facilitation of reaction by bulky substituents adjacent to the reacting group and for several of the *ortho*-effects of aromatic chemistry (Baddeley, *Nature*, 1939, **144**, 444). Later (Baddeley and Chadwick *J.*, 1951, 368), it was shown to account for the slow unimolecular ethanolysis of 1-*o*-tolylethyl chloride relative to that of 1-chloroindane. The carbon skeleton of the latter chloride has essentially the planar configuration required for maximum resonance stabilisation of the corresponding cation and, apart from steric interaction incurred by the chlorine atom, ionisation of this chloride is neither sterically facilitated nor sterically hindered. On the other hand, if we assign to 1-*o*-tolylethyl chloride the preferred configuration (I) in which steric interaction is a minimum, the methyl group of the side-chain being well separated from the plane of the ring (represented by a broken line), its unimolecular solvolysis is hindered (i) by the energy needed to bring this methyl group into or closer to the plane of the ring and (ii) by loss of resonance energy in the corresponding cation should this, from steric causes, be non-planar. Anomalies in reactivity

caused by combination of these two energy terms are difficult to estimate since they are not readily disentangled from inductomeric and electromeric effects.

Hammett and Pfuger (*J. Amer. Chem. Soc.*, 1933, **55**, 4079) showed that a linear relation exists between the logarithm of the rate constants (log k) of one series of reactions and the logarithm of the equilibrium constants (log K) of another distinct series. It is equivalent to a linear relation between the influence of substituents on the free energy of activation in the reactions considered in respect of velocity and their influence on the standard free-energy change between initial and final states in corresponding dissociations (Burkhardt, *Nature*, 1935, **136**, 684; Burkhardt, Ford, and Singleton, *J.*, 1936, 17). Relations of this type have been afforded by reactions of benzene derivatives and, in general, are limited to the field of *meta*- and *para*-derivatives, *i.e.*, to change of substituent in a part of the molecule considerably removed from the reacting group; they demonstrate the similarity between the ways in which composition and structure of a reactant affect rates and equilibria, and "can be reduced to a matter of electron displacements alone" (Hammett, *loc. cit.*). On the other hand, *ortho*-substituents frequently introduce steric factors, operating to different degrees in different reactions and more complex than simple steric hindrance of the type envisaged by Victor Meyer (Hughes, *Quart. Reviews*, 1948, **2**, 107), which provide deviations from the above relation. These deviations are now applied in an attempt to recognise steric hindrance of ionisation of aralkyl chlorides Ar·CRR′Cl; our purpose was served by relating log k for unimolecular solvolysis (reaction *a*) to pK_a for dissociation of the corresponding anilinium ions $Ar\cdot\overset{+}{N}RR'H$ (reaction *b*).



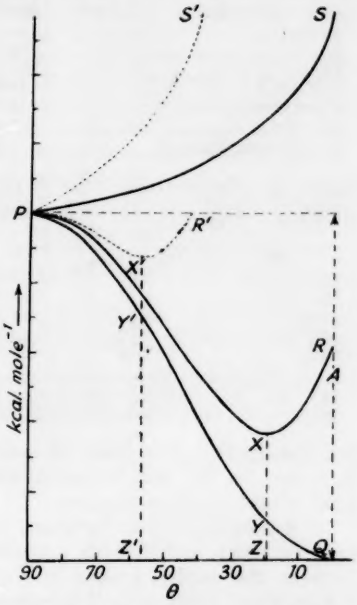
The electron displacements incurred by these two processes are oppositely directed and in general, therefore, *steric effects apart, change in constitution which increases the rate of ionisation, decreases the dissociation; the more basic amines are those which correspond to the*

TABLE 1. *Solvolysis of benzyl chlorides and dissociation of anilinium ions in 50% aqueous ethanol.*

X	X·C$_6$H$_4$·CH$_2$Cl log $10^6k_{83\cdot0}$	X·C$_6$H$_4$·NH$_2$ p$K_{a\ 25\cdot0}$	X	X·C$_6$H$_4$·CH$_2$Cl log $10^6k_{83\cdot0}$	X·C$_6$H$_4$·NH$_2$ p$K_{a\ 25\cdot0}$
p-Me	5·21	5·07	*p*-I	3·87	3·66
p-F	4·45	4·56	*m*-F	3·60	3·50
m-Me	4·33	4·69	*m*-Cl	3·57	3·41
H	4·19	4·58	*m*-Br	3·52	3·38
p-Cl	3·98	3·94	*m*-I	3·49	3·36
p-Br	3·89	3·82	*p*-NO$_2$	0·69	*ca.* 0·9

more reactive chlorides and vice versa; d log k/d pK_a *is positive.* This relation is illustrated in Table 1 by the rates of hydrolysis of several *m*- and *p*-substituted benzyl chlorides in 50% aqueous ethanol at 83·0° (Olivier, *Chem. Revews*, 1935, **16**, 183) and the basic strengths of the corresponding aniline derivatives in 30% aqueous ethanol at 25·0° (Bennett, Brooks, and Glasstone, *J.*, 1935, 1821). It can also apply when the substituent is directly attached to the reacting groups; for example, reactivity increases in the series Ph·CH$_2$Cl < Ph·CHMeCl < Ph·CMe$_2$Cl and basic strength increases in the corresponding series of amines Ph·NH$_2$ < Ph·NHMe < Ph·NMe$_2$ (Bell and Bayles, *J.*, 1952, 1518). (It does not

apply when the substituent, *e.g.*, the phenyl group, can provide electronic displacements directed either towards or away from the reacting group: reactivity *increases* in the series of chlorides $Ph{\cdot}CH_2Cl < Ph_2CHCl < Ph_3CCl$, whereas basic strength *decreases* in the corresponding series of amines $Ph{\cdot}NH_2 > Ph_2NH > Ph_3N$.) On the other hand, since ionisation process (*a*) and dissociation (*b*) incur similar changes in intramolecular configuration, they are probably affected by similar changes in steric interaction: aralkyl chloride and anilinium ion, being comparatively free from mesomeric phenomena, will prefer those configurations in which R and R′, should these be bulky groups, avoid the plane of the benzene ring whereas these groups must lie in or near this plane in the benzyl cation and in the amine if these are to have maximum resonance energy. Thus both reactions are hindered by the increase in steric interaction as R and R′ approach the plane of the ring and by loss of resonance energy in the benzyl cation and in the amine if these, for steric reasons, are not approximately planar. These two energy terms, say for a benzyl cation, are represented graphically in the Figure. Let *P* be the energy content of the ion when mesomeric energy is zero and intra-ionic steric interaction a minimum, *i.e.*, when the angle (θ) between the plane of the side-chain carbonium ion and that of the ring is 90°; and let *PQ*, given by $-A\cos^2\theta$ where *A* is the mesomeric energy when $\theta = 0°$, and *PS* represent the change of mesomeric and of steric interaction respectively with change of θ. Algebraic addition of *PQ* and *PS* provides *PR*, and the minimum at *X* represents the benzyl cation; its energy content is greater by the amount *XZ* than that it would have been if steric interaction were independent of θ; *XZ* is compounded of the energy of steric interaction *XY* and the loss of resonance energy *YZ*. (Change in the curve *PS* or *PQ* will alter the ratio *XY*/*YZ*; *e.g.*, $X'Y'/Y'Z' \neq XY/YZ$.) In this way, incursion of intramolecular steric interaction effects an increase in the energy content of the benzyl cation and, similarly but not equally, in that of the corresponding aromatic amine, and thus hinders ionisation of the benzyl chloride and dissociation of the anilinium ion. *In a series of chlorides and amines in which the members differ mainly in the magnitude of this steric effect, the more basic amines will be those which correspond to the less reactive chlorides and* vice versa; d log *k*/d pK_a *will be negative.* This relation is the opposite of that which usually obtains when this steric effect is absent.



Steric Hindrance of Unimolecular Solvolysis of the Chlorides R·CHPhCl, *where* R *is Methyl, Ethyl, Propyl,* iso*Propyl,* 1-*Ethylpropyl,* tert.-*Butyl and* 1 : 1-*Dimethylpropyl severally.*—These chlorides ionised inconveniently slowly in absolute ethanol, and 80% (by volume) aqueous ethanol was used; increased rate of reaction in solvent of higher dielectric constant or of greater solvating power is typical of the unimolecular solvolysis of such compounds, as also is the progressive diminution in value of the rate coefficient when the extent of reaction exceeds 65—70% (Hughes, Ingold, *et al.*, many papers from 1935). The reactions do not involve rearrangement of side-chain; each chloride was hydrolysed in 50% aqueous acetone and in each instance the corresponding alcohol was isolated and identified; Skell and Hauser (*J. Amer. Chem. Soc.*, 1942, **64**, 2633) had previously demonstrated that unimolecular solvolysis of 1-phenyl*neo*pentyl halides (R = Bu^t) proceeds without rearrangement. Since *neo*pentyl isomerises to the 1 : 1-dimethylpropyl cation (Hughes, Ingold, *et al.*, *J.*, 1946, 192; *Nature*, 1951, **167**, 986; 1951, **168**, 65), the comparative stability of the 1-phenyl*neo*pentyl cation and of the 2 : 2-dimethyl-1-phenylbutyl cation (R = CMe_2Et) is presumably effected by spread of positive charge into the benzene ring.

The kinetic data are assembled in Table 2 while, in Table 3, the reactivities of these chlorides are compared with those of a corresponding series of alkyl chlorides R·CMe_2Cl and with the dissociation constants of corresponding series of aromatic and aliphatic amines R·NHPh and R·NH_2 respectively. Differences between members of a series are greater for the aromatic than for the aliphatic compounds and these greater differences seem to originate largely in differences in magnitude of steric interaction of the side-chain

TABLE 2. *Constants of the Arrhenius equation,* $k = Ae^{-E/RT}$, *for the formation of hydrogen chloride by the solvolysis of the chlorides* R·CHPhCl *in* 80% *aqueous ethanol.*

R	$10^7 k_{45°0}$ (sec.$^{-1}$)	$10^5 k_{65°0}$ (sec.$^{-1}$)	E (kcal./mole)	ΔE	$10^{-10} A$ (sec.$^{-1}$)
Methyl	1180	793	20·4	1	1·0
Ethyl	273	190	20·7	1	0·38
Propyl	327	218	20·3	1	0·24
*iso*Propyl	58·7	50·0	22·9	3·5	2·5
1-Ethylpropyl	145	116	22·3	3	2·3
tert.-Butyl	2·18	2·35	25·4	6	4·8
1 : 1-Dimethylpropyl	4·58	4·64	24·8	5·5	3·9

TABLE 3. *Relative reactivites of the chlorides* R·CHPhCl *and* R·CMe_2Cl *in* 80% *aqueous ethanol, and the dissociation constants of the amines* R·NHPh *and* R·NH_2 *in water at* 25·0°.

	R·CHPhCl (i)		R·CMe_2Cl (ii)		R·NHPh (iii)	R·NH_2 (iv)
R	log $10^5 k_{45°0}$	E	log $ak_{25°0}$	E	pK_a	pK_a
Me	5·07	20·4	5·00	22·2	4·85	10·64
Et	4·44	20·7	5·20	21·0	5·10	10·67
n-Pr	4·51	20·3	5·18	21·2	5·02	10·58
i-Pr	3·77	22·9	4·95	21·4	5·50 (i)	10·63
t-Bu	2·34	25·4	5·08	21·4	7·10	10·45

(i) Determined by potentiometry (see Part II). (ii) Hughes, *loc. cit.*; Hughes *et al.*, *Nature*, 1951, **167**, 987. (iii) Verearschi and Rumpf, *Compt. rend.*, 1949, **228**, 1655; 1949, **229**, 1152. (iv) Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

and the benzene ring since the order of *decreasing* reactivity of the chlorides R·CHPhCl : R = Me, Et, Pr^i, Bu^t is that of increasing basic strength of the amines R·NHPh, *i.e.*, since d log k/d pK_a is negative.

If it is assumed that variation in the value of E (Table 2) is caused wholly by variation in steric effect, and that the magnitude of this effect when R is methyl is the same as that between the methyl groups in *cis*-2-butene (Baddeley and Chadwick, *loc. cit.*), *i.e.*, *ca.* 1 kcal./mole, then steric hindrance of ionisation of these chlorides can be assigned the energy values ΔE in Table 2. Of these values, that for the *tert.*-butyl group (*ca.* 6 kcal./mole) is similar in magnitude to the energy of mesomeric interaction of a phenyl group with an amino-, carbonyl, or vinyl group; this similarity is in accord with evidence of steric hindrance of mesomerism in *N-tert.*-butylaniline (Hickinbottom, *J.*, 1933, 946), pivalophenone (Cherrier, *Compt. rend.*, 1947, **225**, 1306; Ramart-Lucas *et al.*, *Bull. Soc. chim.*, 1937, 481; 1942, 850; 1949, 454; 1952, 422), and α-*tert.*-butylstyrene (Ramart-Lucas, Proc. XIth Intern. Congr. Pure & Appl. Chem., London, 1947, Vol. II, p. 267).

EXPERIMENTAL

Materials.—Chlorides. 1-Phenyl*neo*pentyl alcohol (22 g.) was gradually added with stirring to ice-cold thionyl chloride (44 g.). The mixture was kept overnight and excess of thionyl chloride was removed under reduced pressure. The residue, in ethereal solution, was washed with water and dilute sodium hydrogen carbonate solution, and dried (K_2CO_3). Distillation under nitrogen gave 1-phenyl*neo*pentyl chloride (18 g.), b. p. 71—72°/0·5 mm. This procedure gave the following tabulated chlorides in yields of 70—85%.

Compound R·CHPhCl		Cl (%)	
R	B. p./mm.	Found	Calc.
Methyl	39—40°/0·5	25·2	25·3
Ethyl	61—62°/0·5	23·2	23·2
Propyl	97—98°/10	21·2	21·3
*iso*Propyl	63—64°/0·5	21·1	21·3
1-Ethylpropyl	122—123°/15	18·2	18·3
tert.-Butyl	71—72°/0·5	19·4	19·7
2 : 2-Dimethylpropyl	123—124°/15	18·1	18·3

Alkylphenylcarbinols R·CHPh·OH.—Those with R = methyl, ethyl, and propyl were obtained by reduction of the corresponding ketones with aluminium *iso*propoxide or lithium aluminium hydride; those with R = *iso*propyl, *tert.*-butyl, and 1 : 1-dimethylpropyl were obtained by interaction of benzaldehyde and the appropriate alkylmagnesium halide (Conant and Blatt, *J. Amer. Chem. Soc.*, 1928, **50**, 554; Favorski *et al.*, *Bull. Soc. chim.*, 1936, 239). 2-*Ethyl*-1-*phenylbutan*-1-*ol*, b. p. 126—127°/13 mm. (Found: C, 81·2; H, 10·1. $C_{12}H_{18}O$ requires C, 80·9; H, 10·1%), was similarly obtained; 3-bromopentane, b. p. 116—119°/760 mm., was prepared from pentan-3-ol, b. p. 116—117°/760 mm., which, in turn, was obtained by interaction of ethyl formate and ethylmagnesium bromide.

Solvent.—Aqueous ethanol (80% EtOH by volume) was obtained by addition of distilled water to ethanol which had been purified by the process described by Lund and Bjerrum (*Ber.*, 1931, **64**, 210). One batch of solvent was used throughout.

Determination of Rates of Solvolysis of the Chlorides R·CHPhCl.—(a) *Where* R *was a primary or secondary alkyl group.* A flask was charged with solvent (80 c.c.), fitted with a ground-in stopper, and placed in the thermostat; after *ca.* 0·5 hr., enough freshly distilled chloride was added to provide an approx. 0·05M-solution, and the mixture was shaken vigorously. At selected times, samples (5 c.c.) were pipetted into ice-cold absolute ethanol (50 c.c.) and titrated (bromocresol-green as indicator) with sodium hydroxide solution (0·025N).

(b) *When* R *was a tertiary alkyl group.* The reaction mixture was prepared as above, except that the flask was placed in an ice-water bath; samples (5 c.c.) were pipetted into glass tubes and these were sealed and placed in the thermostat. At selected times, reaction tubes were cooled in ice and water, and their contents were transferred by ethanol (50 c.c.) to a conical flask and titrated as described above.

The rate coefficients were derived from the equation $k = (1/t) \ln (T_\infty - T_0)/(T_\infty - T_t)$, in which the symbols have their usual significance, and are listed in Table 2. Each reaction was duplicated. The experimental errors were less than 3%.

FACULTY OF TECHNOLOGY, MANCHESTER UNIVERSITY. [*Received, January 12th*, 1954.]

Cyto-active Amino-acid and Peptide Derivatives. Part I. Substituted Phenylalanines.

By F. BERGEL and J. A. STOCK.

[Reprint Order No. 5201.]

In a search for more selective tumour inhibitors we have prepared, as a start, some derivatives of phenylalanine. The syntheses of DL-, L-, and D-*p*-di-(2-chloroethyl)aminophenylalanine and of *p*-thioformamido-DL-phenylalanine are described. For the synthesis of the corresponding *p-iso*thiocyanato-compound diethyl α-*p-iso*thiocyanatobenzyl-α-formamidomalonate has been prepared. In biological tests so far carried out, the L-form of the chloroethyl derivative proved the most active.

PRESENT developments in the field of tumour- or leukæmia-inhibiting agents reveal a growing interest in α-amino-acid derivatives. This is, to a considerable extent, due to the occurrence of such units in the molecules of antibiotics and to the discovery of antimetabolite effects with analogues of essential amino-acids. Thus, recent reports disclose tests against neoplastic conditions of a microbiologically produced serine derivative, *O*-diazoacetyl-L-serine (azaserine) (Stock, Reilly, Buckley, Clarke, and Rhoads, *Nature*, 1954, **173**, 71), of a synthetic phenylalanine isostere, thienylalanine (Jacquez, Stock, and Barclay, *Cancer*, 1953, **6**, 828), and of a number of other substances of an amino-acid or peptide nature (cf. Reilly, Stock, Buckley, and Clarke, *Cancer Res.*, 1953, **13**, 684; Brockmann, *Angew. Chem.*, 1954, **66**, 1). Before this trend became noticeable, it had occurred to us that certain natural amino-acids or peptides (either synthetic or isolated from proteins) might,

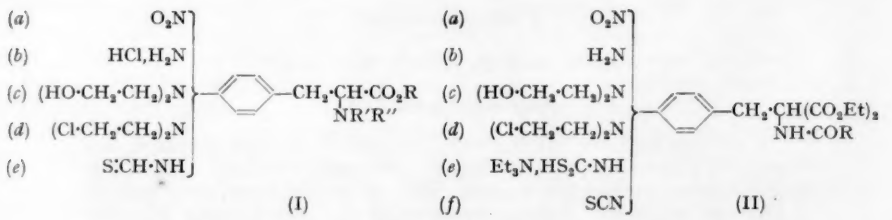
when modified by appropriate groups, show anti-tumour activity, possibly by interaction with cellular constituents in such a manner as to interfere specifically with the nucleic acid or protein metabolism of malignant cells.

Our first approach was greatly stimulated by the systematic work of Ross and his co-workers (see Ross, *Adv. Cancer Res.*, 1953, **1**, 397) on aryldi-(2-chloroethyl)amines. This refers particularly to those carrying additional substituents by which these workers hoped to obtain more pronounced biological specificity. In fact, certain members of a homologous series, $M{\cdot}C_6H_4{\cdot}[CH_2]_n{\cdot}CO_2H$ [where $M = (Cl{\cdot}CH_2{\cdot}CH_2)_2N$; $n = 0$—**4**] (Everett, Roberts, and Ross, *J.*, 1953, 2386) showed greater activity in their inhibition of experimental tumours than did others (Haddow, personal communication).

Although the " nitrogen mustard " group on aromatic systems, evidently acting as an alkylating agent, proved to be a very active cytotoxic radical, it is not unique. Other cyto-active types include diepoxides, ethyleneimines, and methanesulphonates (cf. Ross, *loc. cit.*) and more will no doubt be discovered. In our first set of compounds derived from phenylalanine we made use mainly of the di-(2-chloroethyl)amino-group in the *para*-position. This was done also with the purpose of adding a new variant to the series studied by Everett, Roberts, and Ross (*loc. cit.*). However, with thioformamido- and *iso*thiocyanato-derivatives, we have made a start in modifying the carrier molecule with alternative groupings. It is hoped that these may interfere with abnormal growth by different mechanisms, such as acylation of, or addition to, cellular constituents.

Our syntheses of the *p*-di-(2-chloroethyl)aminophenylalanines followed two routes. One was *via* *p*-nitro-*N*-phthaloylphenylalanine, an intermediate lending itself readily to the preparation of the three optical isomers, and prepared also for subsequent use in peptide synthesis. The second procedure, which is more suitable for the larger-scale preparation of substituted racemic phenylalanine, involved the intermediate preparation of α-acetamido- or α-formamido-α-*p*-nitrobenzylmalonic ester.

The racemic and optically active forms of *p*-nitrophenylalanine were prepared by the method of Erlenmeyer and Lipp (*Annalen*, 1883, **219**, 213), with modifications in the isolation procedure in most experiments. Oxidation with nitric acid confirmed their observation that production of nitro-phenylalanines other than the *p*-substituted one was insignificant.



In the synthesis of the racemic compound the intermediate ethyl *p*-nitro-*N*-phthaloyl-DL-phenylalaninate [*Ia*; R = Et, R′R″ = *o*-$C_6H_4(CO)_2$] was prepared by heating *p*-nitro-DL-phenylalanine with phthalic anhydride alone (cf. Billman and Harting, *J. Amer. Chem. Soc.*, 1948, **70**, 1473) or in pyridine (cf. King and Kidd, *J.*, 1949, 3315) and esterifying the product in ethanolic hydrogen chloride. With the optically active isomers, however, in order to avoid racemisation, another method due to King and Kidd (*loc. cit.*), used in their case to prepare ethyl phthaloyl-L-glutamate, was followed. After a successful trial with the DL-compound, phthalic anhydride was allowed to react with the ethyl esters of *p*-nitro-L- and -D-phenylalaninate severally in benzene solution at room temperature. The resulting *N*-*o*′-carboxybenzoyl-*p*-nitro-L- and -D-phenylalanine esters were converted into the corresponding *N*-phthaloyl derivatives [*Ia*; R = Et, R′R″ = *o*-$C_6H_4(CO)_2$] by refluxing ethanolic hydrogen chloride. The three isomeric phthaloyl esters were reduced catalytically and the *p*-amino-compounds obtained as their hydrochlorides [*Ib*; R = Et, R′R″ = *o*-$C_6H_4(CO)_2$]. In the case of the DL-isomer the free base was characterised. Hydroxy-

ethylation and conversion into the di-(2-chloroethyl)amino-derivatives (I*d*; R = R′ = R″ = H) followed conventional methods except that in the final hydrolysis of the chlorinated optically active products, 6N-hydrochloric acid was used instead of the concentrated acid in order to minimise the risk of racemisation. The specific rotation of *p*-di-(2-chloroethyl)amino-D-phenylalanine was not significantly altered when the compound was subjected to the hydrolysis conditions used in the final stage of preparation, a result in line with the known stability of optically active amino-acids in acid media (cf. Neuberger, *Adv. Protein Chem.*, 1948, **4**, 297). This fact did not, however, eliminate the possibility of partial racemisation during the hydrolysis of the phthaloyl and ester groups. As a check, therefore, L-phenylalanine was taken through the same cycle of reactions *via* the ethyl ester of *N*-*o*′-carboxybenzoyl-L-phenylalanine and the *N*-phthaloyl ester, back again to the L-amino-acid. The starting material had $[\alpha]_D^{21}$ −6·9° ± 0·3° and the final product $[\alpha]_D^{21}$ −7·0° ± 0·3° (both in N-hydrochloric acid); so no detectable racemisation had occurred. In this experiment, the hydrolysis of the *N*-phthaloyl-L-phenylalanine ester was much slower than that of the corresponding *p*-di-(2-chloroethyl)amino-compound.

The same cycle of reactions was not tried with the optically active " nitrogen mustards " themselves since these were available only in relatively small amounts which were reserved for biological testing.

No attempt was made to ensure that the L- and D-phenylalanines employed as starting materials were optically pure. This was justified by the fact that the intermediate *p*-nitro-*N*-phthaloyl-L- and -D-phenylalanine esters [I*a*; R = Et, R′R″ = *o*-$C_6H_4(CO)_2$] were readily obtained in their optically pure forms of $[\alpha]_D^{20}$ −207° and +207° respectively, showing that contaminating isomer had been removed during the preceding stages.

The free di-(2-chloroethyl)amino-substituted amino-acids (I*d*; R = R′ = R″ = H) were obtained by precipitation with sodium acetate from the aqueous solutions of their hydrochlorides. The L- and the D-acid each crystallised from methanol with one molecule of solvent of crystallisation, had m. p. 182° and $[\alpha]_D^{23}$ +7·5°, $[\alpha]_D^{21}$ −7·5° respectively in N-hydrochloric acid.

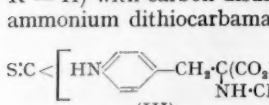
As indicatedabove, the DL-derivative (I*d*; R = R′ = R″ = H) was also synthesised by preparing first α-acetamido- or α-formamido-α-*p*-nitrobenzylmalonic ester (II*a*; R = Me or H). Catalytic reduction gave the corresponding amino-compounds (II*b*; R = Me or H) and treatment with ethylene oxide the di-(2-hydroxyethyl)amino-derivatives (II*c*; R = Me or H). While chlorination with phosphorus oxychloride did not work well here, the use of thionyl chloride with short refluxing in chloroform led, after hydrolysis and decarboxylation with hydrochloric acid, to a relatively good yield of (I*d*; R = R′ = R″ = H). The formamido-intermediate (II*d*; R = H) showed less tendency to darken during chlorination and gave a cleaner hydrolysate than did the acetamido-compound (II*d*; R = Me).

In order to ascertain the reactivity of *p*-di-(2-chloroethyl)amino-DL-phenylalanine as compared with other aromatic " nitrogen mustards," the compound was hydrolysed by Ross's method (*J.*, 1949, 183). Titration of hydrogen ion was carried out electrometrically since the usual method using phenolphthalein as indicator was unsatisfactory. The result indicated a 21% decomposition of the 2-chloroethyl group. Chloride-ion determination showed that 22% of the halogen was liberated, a result in accord with the acidity determination. The hydrolysis rate is of the same order as that of other aryl-*p*-di-(2-chloroethyl)-amines of known biological activity (cf. Ross, *loc. cit.*, 1953).

p-Thioformamido-DL-phenylalanine was prepared by the action of sodium dithioformate on *p*-amino-DL-phenylalanine in aqueous solution (cf. Todd, Bergel, Karimullah, and Keller, *J.*, 1937, 361). The crystalline product, analysis of which indicated a monothioformamido-derivative, had no definite melting point. In order to ascertain which of the two amino-groups had been thioformylated we converted the thio-compound into the corresponding formamido-compound by refluxing aqueous formic acid. The product melted at 227—229° (decomp.), and was clearly different from *p*-amino-N^{α}-formyl-DL-phenylalanine, m. p. 168—169°, prepared by hydrogenation of *N*-formyl-*p*-nitro-DL-phenylalanine. The thioformamido-compound was therefore assigned structure (I*e*; R = R′ = R″ = H).

In our attempt to prepare *p-iso*thiocyanato-DL-phenylalanine, we again made use of the malonic acid synthesis. The reaction of α-*p*-aminobenzyl-α-formamidomalonic ester (II*b*;

R = H) with carbon disulphide and triethylamine in ethanol led to the expected triethylammonium dithiocarbamate (II*e*; R = H) (cf., *e.g.*, Dains, Brewster, and Olander, *Org. Synth.*, Coll. Vol. I, 1932, p. 437). A by-product of this reaction was the symmetrically disubstituted thiourea (III), m. p. 182—183°. Its structure was confirmed by the identity of the compound with the product obtained by condensing diethyl *p*-aminobenzylformamidomalonate (II*b*; R = H) with diethylformamido-*p*-*iso*-thiocyanatobenzylmalonate (II*f*; R = H; see below).



(III)

When the dithiocarbamate was allowed to react with ethyl chloroformate in dioxan solution at room temperature (cf. Andreasch, *Monatsh.*, 1906, **27**, 1211) diethyl formamido-*p*-*iso*thiocyanatobenzylmalonate (II*f*; R = H) was obtained directly, the presumed intermediate carbonic–dithiocarbamic mixed anhydride decomposing spontaneously under our conditions (cf. Johnson and Ticknor, *Proc. Nat. Acad. Sci.*, 1917, **3**, 303). Attempts to hydrolyse the *iso*thiocyanatomalonate to the *iso*thiocyanatophenylalanine have so far been unsuccessful.

The three optically isomeric *p*-di-(2-chloroethyl)phenylalanines, carrying the experimental numbers CB 3007, 3025, and 3026 respectively, have been submitted to tests on rats carrying the Walker carcinoma 256. Details will be published elsewhere by Professor A. Haddow to whom thanks are due for his interest in this work and for his permission to refer to his biological results. Under his experimental conditions the L-isomer has shown the greatest effect, 1 mg./kg. producing complete inhibition of the tumours. This is in conformity with the results of Stock *et al.* (*loc. cit.*) who found that of the three azaserines the L-isomer showed maximum activity against mouse sarcoma 180.

Experimental

p-*Nitro*-DL-, -L-, *and* -D-*phenylalanine* (I*a*; R = R′ = R″ = H).—(*a*) Erlenmeyer and Lipp's method (*loc. cit.*) was employed several times for the DL-compound but the yields were lower than claimed by them and were in general about 80%.

(*b*) A satisfactory simplification of method (*a*) avoided the use of lead carbonate and hydrogen sulphide. In one experiment DL-phenylalanine (12·5 g.) was nitrated in the usual way and the viscous mixture poured into cold water (500 ml.) with stirring. A slight excess of diluted aqueous ammonia was added and the solution evaporated until solid began to appear. The cooled mixture gave *p*-nitro-DL-phenylalanine in 90% yield, the first crop having m. p. 240—243° (decomp.) and the second m. p. 235—240° (decomp.) after recrystallisation from water.

L-Phenylalanine {3·9 g.; $[\alpha]_D^{25}$ −33·5° ± 0·5° (*c*, 1·94 in H_2O)} was nitrated and the product (84%) isolated in the same way. Recrystallisation from water gave colourless needles of p-*nitro*-L-*phenylalanine monohydrate*, m. p. 238—241° (decomp.; softening at 230°), $[\alpha]_D^{25}$ +9·8° ± 0·3° (*c*, 1·77 in N-HCl) (Found: C, 47·3; H, 5·3; N, 12·8. $C_9H_{19}O_4N_2,H_2O$ requires C, 47·4; H, 5·3; N, 12·3%).

Similarly, D-phenylalanine {2·95 g.; $[\alpha]_D^{22}$ +31·5° ± 0·5° (*c*, 1·18 in H_2O); prepared by resolution of DL-phenylalanine by Fischer and Schoeller's method (*Annalen*, 1907, **357**, 4, 7)} was nitrated in 88% yield. Recrystallisation from water (charcoal) gave almost colourless needles of p-*nitro*-D-*phenylalanine monohydrate*, m. p. 238—240° (decomp.), $[\alpha]_D^{20}$ −8·9° ± 0·3° (*c*, 2·41 in N-HCl) (Found: C, 47·2; H, 5·4; N, 12·4%).

(*c*) An ion-exchange resin was employed in another method. The acid mixture from the nitration of DL-phenylalanine (11·05 g.) was poured into water (800 ml.), and the solution added to a mechanically stirred slurry of Amberlite IR-4B resin (wet wt. 300 g.) and water (500 ml.). Stirring was continued until the pH had risen to about 5 (approx. 15 min.). Evaporation of the combined filtrate and washings gave *p*-nitro-DL-phenylalanine in 80% yield.

Oxidation of Nitro-DL-*phenylalanine.*—The nitration product (0·485 g.), m. p. 240—243° (decomp.), prepared as in (*a*) above, was heated with concentrated nitric acid (4·5 ml.) and water (10·5 ml.) for 4 hr. at 180°. The tube was cooled in an acetone–solid carbon dioxide bath before being opened. Yellow plates of *p*-nitrobenzoic acid, m. p. 240—243°, were obtained in 83% yield.

p-*Nitro*-N-*phthaloyl*-DL-*phenylalanine* [I*a*; R = H, R′R″ = *o*-$C_6H_4(CO)_2$].—(*a*) In one experiment, *p*-nitro-DL-phenylalanine (10·0 g.) was refluxed with phthalic anhydride (7·05 g., 1·00 mol.) in dry pyridine (75 ml.) for 1·5 hr. (cf. King and Kidd, *loc. cit.*). The solution was concentrated to small bulk (vacuum; steam-bath), and the residue refluxed for 5 min. with acetic anhydride (25 ml.). The cooled liquid yielded a sticky solid when poured into water (250

ml.), and further precipitation occurred when the mixture was acidified to Congo-red with hydrochloric acid. The washed product (96%) became granular when rubbed. Two successive crystallisations from chloroform–light petroleum yielded the *N-phthaloyl*-DL-compound as colourless needles, m. p. 180—181° (Found: C, 59·6; H, 3·8; N, 8·2. $C_{17}H_{12}O_6N_2$ requires C, 60·0; H, 3·55; N, 8·2%).

(*b*) *p*-Nitro-DL-phenylalanine (2·10 g.) and powdered phthalic anhydride (1·48 g., 1·00 mol.) were mixed and heated in a Pyrex tube at 170—190° for 15 min. (cf. Billman and Harting, *loc. cit.*). The brown mass crystallised from aqueous ethanol (charcoal) in colourless needles (86%), m. p. 177—178° rising to 179—180° when recrystallised from chloroform–light petroleum; the product had a mixed m. p. of 180—181° with the analytical specimen of *p*-nitro-*N*-phthaloyl-DL-phenylalanine described under (*a*).

Ethyl Esters of p-*Nitro*-N-*phthaloyl*-DL-, -L-, *and* -D-*phenylalanine* [I*a*; R = Et, R′R″ = *o*-$C_6H_4(CO)_2$].—(*a*) Crude *p*-nitro-*N*-phthaloyl-DL-phenylalanine [16·7 g.; prepared as in (*a*) above] was esterified by refluxing it for 1·5 hr. in saturated ethanolic hydrogen chloride. The product, crystallised from *n*-propanol, had m. p. 91—93°. Two successive crystallisations from propanol (charcoal) gave colourless prisms of the DL-*ester*, m. p. 96·5—97° (Found: C, 61·7; H, 4·4; N, 7·6. $C_{19}H_{16}O_6N_2$ requires C, 61·95; H, 4·4; N, 7·6%).

(*b*) (i) p-*Nitro*-DL-, -L-, *and* -D-*phenylalanine ethyl ester hydrochlorides*. The DL-ester hydrochloride was prepared in 82% yield by refluxing a solution of the nitro-amino-acid in 3·5N-ethanolic hydrogen chloride, evaporating the product, and recrystallising the residue from acetone–methanol. Recrystallisation gave almost colourless needles of the hydrochloride, m. p. 185—186° (Found: C, 48·6; H, 5·8; N, 10·0. Calc. for $C_{11}H_{15}O_4N_2Cl$: C, 48·1; H, 5·5; N, 10·2%). Dornow and Winter (*Chem. Ber.*, 1951, **84**, 307) prepared the same compound by hydrolysis and decarboxylation of diethyl formamido-*p*-nitrobenzylmalonate and subsequent esterification. They recorded m. p. 179—180°. The optical isomers were prepared similarly. From *p*-nitro-L-phenylalanine (2·50 g.) was obtained p-*nitro*-L-*phenylalanine ethyl ester hydrochloride* (83%) in colourless rods (from dioxan–ethyl acetate), m. p. 207—208° (decomp.), $[\alpha]_D^{25}$ +12·7° ± 0·3° (*c*, 2·24 in H_2O) (Found: C, 47·95; H, 5·55; N, 10·3. $C_{11}H_{15}O_4N_2Cl$ requires C, 48·1; H, 5·5; N, 10·2%). Esterification of the D-isomer (3·0 g.) gave, in comparable yield, colourless rods (from dioxan–ethyl acetate) of p-*nitro*-D-*phenylalanine ethyl ester hydrochloride*, m. p. 204—205°, $[\alpha]_D^{20}$ −12·0° ± 0·3° (*c*, 2·06 in H_2O) (Found: C, 48·2; H, 5·7; N, 10·1%).

(ii) *Ethyl esters of* N-*o*′-*carboxybenzoyl*-p-*nitro*-DL-, -L-, *and* -D-*phenylalanine* (I*a*; R = Et, R′ = H; R″ = *o*-CO·C_6H_4·CO_2H) (cf. King and Kidd, *loc. cit.*). *p*-Nitro-DL-phenylalanine ethyl ester hydrochloride (1·00 g.) was suspended in dry benzene (8 ml.), and diethylamine (0·27 g., 1·00 mol.) was added. The mixture was shaken until all the ester hydrochloride crystals had dissolved. Dry ether was added to the turbid liquid until precipitation was complete, the diethylamine hydrochloride filtered off, and the filtrate evaporated almost to dryness under vacuum. The oily residue was taken up in dry benzene (15 ml.) and powdered phthalic anhydride (0·54 g., 1·00 mol.) added with shaking. In less than a minute, the mixture suddenly thickened to a white pasty mass and its temperature rose. The mixture was evaporated under vacuum. The residue crystallised from acetone–light petroleum in colourless crystals of N-*o*′-*carboxybenzoyl*-p-*nitro*-DL-*phenylalanine ethyl ester* (93%), m. p. 181° (Found: C, 59·1; H, 4·9; N, 7·4. $C_{19}H_{18}O_7N_2$ requires C, 59·1; H, 4·7; N, 7·25%).

Ethyl *p*-nitro-L-phenylalaninate hydrochloride (1·90 g.) gave, after similar treatment, a 94% yield of colourless needles (from acetone–light petroleum) of the L-*carboxybenzoyl* compound m. p. 180—182°, $[\alpha]_D^{23}$ +19·4° ± 0·3° (*c*, 2·94 in dioxan) (Found: C, 59·1; H, 4·7; N, 7·3%).

From *p*-nitro-D-phenylalanine ethyl ester hydrochloride (2·15 g.) were obtained colourless needles (93%) of N-*o*′-*carboxybenzoyl*-p-*nitro*-D-*phenylalanine ethyl ester*, m. p. 180—181°, $[\alpha]_D^{21}$ −19·7° ± 0·3° (*c*, 3·91 in dioxan) (Found: C, 58·9; H, 4·9; N, 7·2%).

(iii) *Ring closure of the* DL-, L-, *and* D-*carboxybenzoyl compounds*. The DL-compound (1·10 g.) was refluxed for 1·5 hr. with ethanolic 3·5N-hydrogen chloride (25 ml.). Removal of the solvent gave a pale yellow gum (1·08 g.) which crystallised from *n*-propanol in colourless prisms of *p*-nitro-*N*-phthaloyl-DL-phenylalanine ethyl ester (86%), m. p. 96·5—97·5°, undepressed on admixture with the compound of m. p. 96·5—97° prepared as under (*a*) above.

The corresponding L-*isomer* was prepared similarly from the L-carboxybenzoyl compound (1·85 g.), except that ethanolic 2N-hydrogen chloride was used. The product crystallised readily in 85% yield from amyl alcohol in colourless prisms, m. p. 80—81°, $[\alpha]_D^{23}$ −207° ± 1° (*c*, 1·15 in dioxan) (Found: C, 61·7; H, 4·5; N, 7·5%).

In the same way, the ethyl ester of *N-o*′-carboxybenzoyl-*p*-nitro-D-phenylalanine (2·18 g.) yielded the corresponding D-*isomer* (88%), m. p. 78—80° (from amyl alcohol). This recrystal-

lised from methanol in colourless prisms, m. p. 79—80°, $[\alpha]_D^{20}$ +207° ± 1° (*c*, 1·72 in dioxan). After a further recrystallisation from amyl alcohol, the m. p. and specific rotation of the product were unchanged (Found: C, 61·4; H, 4·7; N, 7·8%).

p-*Amino*-N$^{\alpha}$-*phthaloyl*-DL-, -L-, *and* -D-*phenylalanine Ethyl Ester Hydrochlorides* [*Ib*; R = Et; R′R″ = *o*-$C_6H_4(CO)_2$].—The DL-nitro-compound (9·0 g.) was hydrogenated at atmospheric pressure in ethyl acetate–methanol over palladium–calcium carbonate. The orange gum obtained on evaporation of the filtrate was converted into the hydrochloride (93%) in ether. Two successive crystallisations from ethyl acetate–acetone gave slightly tinted needles of the DL-*amine hydrochloride*, m. p. 205—207° (decomp.) (Found: N, 7·4; Cl, 9·3. $C_{19}H_{19}O_4N_2Cl$ requires N, 7·5; Cl, 9·5%).

The corresponding L-nitro-compound (1·30 g.) was converted into the amine salt (96%) in the same way, and was recrystallised from dioxan–ethyl acetate, giving colourless needles of the L-*amine hydrochloride*, m. p. 234—235° (decomp.; slight softening at 215°), $[\alpha]_D^{22}$ −153° ± 1° [*c*, 0·945 in 3 : 1 (by vol.) H_2O–EtOH] (Found: N, 7·3%).

The D-*amine hydrochloride* was prepared in an analogous manner in 88% yield as needles (from dioxan–ethyl acetate), m. p. 233—234° (decomp.), $[\alpha]_D^{22}$ +157° ± 1° [*c*, 1·01 in 3 : 1 (by vol.) H_2O–EtOH] (Found: N, 7·1%).

Isolation of the free DL-*base*. Excess of dilute aqueous ammonia was added to a warm, opalescent, filtered aqueous solution of the DL-amine hydrochloride (1·83 g.). The precipitated gum was washed with water and crystallised from aqueous methanol, giving large pale yellow needles, m. p. 109—111°. Recrystallisation yielded faintly tinted needles of p-*amino*-N$^{\alpha}$-*phthaloyl*-DL-*phenylalanine ethyl ester*, m. p. 110—112° (Found: N, 8·3. $C_{19}H_{18}O_4N_2$ requires N, 8·3%).

p-*Di*-(2-*chloroethylamino*)-DL-, -L-, *and* -D-*phenylalanine* (*Id*; R = R′ = R″ = H) (cf. Everett *et al.*, *loc. cit.*).—(*a*) *p*-Amino-*N*-phthaloyl-DL-phenylalanine ethyl ester (1·00 g.) was suspended in water (12 ml.), and glacial acetic acid was added with stirring until dissolution was complete (about 8 ml. of acid were required). Ethylene oxide (2 ml.) was added with shaking and the mixture kept for 24 hr. at room temperature. The clear yellow solution was poured into water (100 ml.), a slight excess of sodium hydrogen carbonate carefully added with stirring, the gummy precipitate extracted with ethyl acetate, and the dried ($MgSO_4$) solution evaporated to dryness on a steam-bath. The clear yellow gummy *p*-di-(2-hydroxyethyl)-amino-N$^{\alpha}$-phthaloyl-DL-phenylalanine ethyl ester did not crystallise.

The DL-di(hydroxyethyl)amino-compound (6·0 g.), prepared as above, was dissolved in benzene (100 ml.), and the solution was dried by distilling off part (25 ml.) of the solvent. Freshly distilled phosphorus oxychloride (15 ml.) was added and the mixture refluxed for 25 min. The solution was evaporated to dryness under vacuum and the clear gummy residue refluxed with concentrated hydrochloric acid for 6 hr. The pink solution was filtered from the red-tinted phthalic acid (whose identity was checked through the toluidide, m. p. and mixed m. p. 199—201°) and evaporated to small bulk under vacuum. Addition of concentrated sodium acetate solution precipitated a white granular solid which crystallised from methanol in tiny colourless needles of p-*di*-(2-*chloroethyl*)*amino*-DL-*phenylalanine*, m. p. 180—181° (46%, calculated on the free amino-compound) (Found: C, 51·1; H, 6·0; N, 8·9; Cl, 23·2. $C_{13}H_{18}O_2N_2Cl_2$ requires C, 51·1; H, 5·9; N, 8·5; Cl, 23·3%). The L-*isomer* was obtained similarly, starting from the unpurified free base obtained by ammonia treatment of *p*-amino-N$^{\alpha}$-phthaloyl-L-phenylalanine ethyl ester hydrochloride (1·06 g.). The chlorination product was refluxed for 3·5 hr. with 6N-hydrochloric acid. Precipitation with sodium acetate and crystallisation from methanol gave small colourless needles of monosolvated amine (37·5%, calc. on the amine hydrochloride), m. p. 182—183° (decomp.), $[\alpha]_D^{22}$ +7·5° ± 0·5° (*c*, 1·33 in N-HCl), $[\alpha]_D^{22}$ −31·5° ± 0·5° (*c*, 0·67 in MeOH) (Found: N, 8·3; Cl, 21·1. $C_{13}H_8O_2N_2Cl_2$,MeOH requires N, 8·3; Cl, 21·3%).

In the same way, the D-hydrochloride (1·15 g.) yielded colourless needles of monosolvated D-*base* (34%), m. p. 181·5—182° (decomp.), $[\alpha]_D^{21}$ −7·5° ± 0·5° (*c*, 1·26 in N-HCl) (Found: N, 8·6; Cl, 21·2%).

(*b*) Thionyl chloride (2 ml.) was added to a solution of diethyl α-acetamido-α-*p*-di-(2-hydroxyethyl)aminobenzylmalonate (1·38 g.) (see below) in dry alcohol-free chloroform (25 ml.). The clear solution was refluxed for 10 min. by which time it had begun to darken appreciably. It was evaporated under vacuum, and the residual gum refluxed with concentrated hydrochloric acid (20 ml.) for 3 hr. The method of isolation was as described above, and crystallisation of the product from methanol gave the di(chloroethyl)amine, m. p. 179—180° (decomp.), undepressed on admixture with material prepared from DL-phenylalanine, in 63% yield.

The corresponding hydroxyethylated formamido-compound (1·0 g.) was chlorinated as

described in (*a*). In this case, however, there was no tendency to darken during the thionyl chloride treatment. Evaporation of the chloroform solution yielded a pale yellow granular solid which was refluxed with hydrochloric acid for 40 min. only. The chloro-compound (74%), m. p. 182° (decomp.), had a mixed m. p. of 180° (decomp.) with the material of m. p. 179—180° obtained as under (*a*).

*Diethyl α-Formamido-α-*p*-nitrobenzylmalonate* (II*a*; R = H)*.—Condensation of *p*-nitrobenzyl chloride (9·75 g.) and diethyl formamidomalonate (13·0 g., 1·12 mol.) was carried out as described by Dornow and Winter (*Chem. Ber.*, 1951, **84**, 307) except that the mixture was heated under reflux for 2 hr. The residue obtained on filtration of the hot reaction mixture crystallised from aqueous ethanol in colourless rods (13·6 g.) of *diethyl formamido-*p*-nitrobenzylmalonate*, m. p. 190°. The filtrate from the reaction mixture deposited the same compound (0·83 g., total yield, 75%), m. p. 189—190° (Found: C, 53·6; H, 5·5; N, 8·3. $C_{15}H_{18}O_7N_2$ requires C, 53·25; H, 5·4; N, 8·3%).

*Diethyl α-*p*-Aminobenzyl-α-formamidomalonate* (II*b*; R = H).—Diethyl formamido-*p*-nitrobenzylmalonate (4·0 g.) was hydrogenated over palladium–calcium carbonate in suspension in ethyl acetate–methanol. The nitro-compound went into solution as reduction proceeded and the *p-aminobenzyl-formamidomalonate* crystallised in colourless needles (94%), m. p. 131—132° from ethyl acetate–light petroleum (Found: C, 58·3; H, 6·6; N, 9·2. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%).

*Diethyl α-Acetamido- and α-Formamido-*p*-di-(2-hydroxyethyl)aminobenzylmalonate* (II*c*; R = Me or H).—Diethyl acetamido-*p*-aminobenzylmalonate (Elliott and Harington, *J.*, 1949, 1374) (3·84 g.) was hydroxyethylated with ethylene oxide (6 ml.) in 25% aqueous acetic acid (40 ml.) at room temperature (17 hr.). The product was worked up in the usual way. Crystallisation from ethyl acetate gave colourless needles of *diethyl acetamido-*p*-di-(2-hydroxyethyl)-aminobenzylmalonate* (82%), m. p. 100° (Found: C, 58·3; H, 7·5; N, 6·7. $C_{20}H_{30}O_7N_2$ requires C, 58·5; H, 7·4; N, 6·8%).

Hydroxyethylation of the formamido-compound (2·80 g.) led similarly to *diethyl α-*p*-di-(2-hydroxyethyl)aminobenzyl-α-formamidomalonate* (83%), m. p. 118°, rising to 120·5° on recrystallisation from ethyl acetate–light petroleum (Found: C, 57·4; H, 7·3; N, 7·1. $C_{19}H_{28}O_7N_2$ requires C, 57·6; H, 7·1; N, 7·1%).

Racemisation Experiments.—(*a*) *p*-Di-(2-chloroethyl)amino-D-phenylalanine (33 mg.) in 6N-hydrochloric acid (1·5 ml.) had $[\alpha]_D^{22}$ −4·75° ± 0·25° (*c*, 2·2). The solution was heated in a sealed tube for 3·5 hr. in refluxing 6N-hydrochloric acid, after which $[\alpha]_D^{22}$ was −4·5° ± 0·25°.

(*b*) L-Phenylalanine {0·600 g.; $[\alpha]_D^{21}$ −6·9° ± 0·3° (*c*, 1·68 in N-HCl)} was converted into the ester hydrochloride by refluxing ethanolic 2N-hydrogen chloride for 2 hr. The free ester, obtained from the hydrochloride (0·500 g.; acetone-crystallised) by diethylamine treatment, was allowed to react in benzene solution with phthalic anhydride (0·33 g., 1·00 mol.). After 2 days, the clear solution was evaporated, and the gummy residue taken up in ether. Crystallisation set in on cooling, and recrystallisation of the product from acetone–light petroleum gave colourless needles of *N-o′-carboxybenzoyl-*L*-phenylalanine ethyl ester*, m. p. 119—120°, $[\alpha]_D^{20}$ +31·0° ± 0·5° (*c*, 1·56 in dioxan) (Found: C, 66·8; H, 5·5; N, 4·3. $C_{19}H_{19}O_5N$ requires C, 66·85; H, 5·6; N, 4·1%).

The carboxybenzoyl compound (0·50 g.) was refluxed with ethanolic 2N-hydrogen chloride for 1·75 hr. The gummy residue obtained by evaporation of the solution was refluxed with 6N-hydrochloric acid (10 ml.) for 2·5 hr. A considerable quantity of oil was present at this stage. The mixture was evaporated to dryness under vacuum, concentrated hydrochloric acid (7 ml.) was added to the residue, and refluxing continued for a further hour. Much oil remained at the end of this period. The mixture was cooled and kept overnight in the ice box. Water (10 ml.) was added and the mixture shaken to take up any phenylalanine hydrochloride which may have crystallised. The filtrate was evaporated to dryness (vacuum), and the residue taken up in a little water and filtered. The crystalline residue from the evaporated filtrate was recrystallised from acetone–methanol and gave colourless rhombic crystals of L-phenylalanine hydrochloride (0·025 g.), $[\alpha]_D^{21}$ −7·0° ± 0·3° (*c*, 1·37, calc. as free amino-acid, in N-HCl).

Hydrolysis in 1 : 1 Acetone–Water at 66° (cf. Ross, *J.*, 1949, 183).—*p*-Di-(2-chloroethyl)-phenylalanine (0·076 g., 0·25 mmole) was refluxed in " AnalaR " acetone (12·5 ml.)–water (12·5 ml.) for 30 min. The cooled solution was titrated electrometrically (Pye pH meter, model 605) against 0·1N-sodium hydroxide. An unhydrolysed solution in the same medium was titrated similarly. The shift in the titration curve corresponded to 21% hydrolysis.

* [*Added in Proof.*]—This compound has recently been characterised by Schlögl, Wessely, and Korger (*Monatsh.*, 1952, **83**, 845).

Liberation of chloride ion was determined as follows. A hydrolysate obtained simultaneously with and exactly as the above was cooled and set aside for 0·5 hr. (during the titration of the other solution). 0·1N-Silver nitrate (5·0 ml.) and a few drops of 2N-nitric acid were added. The mixture was shaken for 1—2 min., the silver chloride was filtered off, and the filtrate and washings were titrated against 0·1N-potassium thiocyanate in presence of ferric ammonium sulphate. This indicated 22% hydrolysis.

p-*Thioformamido*-DL-*phenylalanine* (I*e*; R = R′ = R″ = H).—A filtered solution of sodium dithioformate (0·35 g.) in water (2 ml.) was added to a solution of *p*-amino-DL-phenylalanine (0·180 g.) in water (10 ml.). After 20 min. crystals began to separate from the yellow solution. The mixture was kept at room temperature for 2 hr. and was then placed in the ice-box for a further 2 hr. The product (81%) recrystallised from water as pale yellow rods of the monohydrated *thioformamido*-compound (indefinite decomp. temp.; began to char at 210°) (Found: C, 49·6; H, 5·9; N, 11·5; S, 13·4. $C_{10}H_{12}O_2N_2S,H_2O$ requires C, 49·6; H, 5·8; N, 11·6; S, 13·2%).

p-*Formamido*-DL-*phenylalanine*.—The thioformamido-derivative (0·155 g.) was refluxed in 98% formic acid (3 ml.) and water (6 ml.) until evolution of hydrogen sulphide ceased (about 1·5 hr.). The solution was evaporated to dryness under reduced pressure. A little water was added to the colourless residue, and the solution again evaporated to dryness to remove traces of formic acid. The residue was twice crystallised from aqueous ethanol, yielding very small needles of p-*formamido*-DL-*phenylalanine* (75%), m. p. 227—229° (decomp.) (Found: C, 57·3; H, 6·0; N, 13·2. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%).

N-*Formyl*-p-*nitro*-DL-*phenylalanine* (cf. Waley, *Chem. and Ind.*, 1953, 107).—*p*-Nitro-DL-phenylalanine (1·90 g.) was dissolved in 98% formic acid (15 ml.), and acetic anhydride (5 ml.) was added. The solution was kept at 45—55° for 30 min., then water (50 ml.) was added slowly with stirring and warming. Crystallisation began on cooling. The mixture was left in the ice-box overnight and yielded pale yellow prisms (75%) of the N-*formyl* compound, m. p. 185—186°, raised to 187° on recrystallisation from water (Found: C, 50·3; H, 4·2; N, 11·5. $C_{10}H_{10}O_5N_2$ requires C, 50·4; H, 4·2; N, 11·8%).

p-*Amino*-N-*formyl*-DL-*phenylalanine*.—The *p*-nitro-compound (0·60 g.) was hydrogenated at room temperature and pressure in water (30 ml.) over a 5% palladium–charcoal catalyst. Reduction was complete in about an hour. Evaporation of the filtrate gave a gum which crystallised from ethanol and in a 77% yield of the reduction product. Recrystallisation from ethanol (charcoal) gave colourless prisms of p-*amino*-N-*formyl*-DL-*phenylalanine*, m. p. 168—169° (decomp.) (Found: C, 57·4; H, 6·1; N, 13·2. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%).

Reduction of the nitro-compound over palladium–calcium carbonate gave a granular product which was twice precipitated from its aqueous solution by addition of ethanol. Analysis of the compound, which gave an ash on ignition, showed it to be the *calcium salt* of *p*-amino-N-formyl-DL-phenylalanine, m. p. 316—318° (decomp.) (Found: N, 12·3. $C_{20}H_{22}O_6N_4Ca$ requires N, 12·3%).

Reaction of Diethyl p-*Aminobenzylformamidomalonate with Carbon Disulphide and Triethylamine*.—A sealed tube containing the malonate (6·0 g.), carbon disulphide (2·0 ml., 2·0 mol.), and triethylamine (4·0 ml., 2·9 mol.) in ethanol (40 ml.) was heated in a water bath at 70° for 10 min. and then allowed to cool slowly (30 min.) to room temperature. The filtered solution was left in the ice-box overnight. The pale yellow crystalline product (6·60 g.), m. p. 114—115° (decomp.), was recrystallised from *n*-propanol and gave yellow prisms (2·63 g.) of *triethylammonium* N-p-(*di*-2-*ethoxycarbonyl*-2-*formamidoethyl*)*phenyldithiocarbamate* (II*e*; R = H), m. p. 106° (decomp.), unchanged on recrystallisation from propanol. The fall in m. p. on the first recrystallisation was noticed also in a second experiment (Found: C, 54·4; H, 6·9; N, 8·4; S, 13·1. $C_{22}H_{35}O_5N_3S_2$ requires C, 54·4; H, 7·3; N, 8·7; S, 13·2%).

The ethanolic mother-liquor from the crude dithiocarbamate was evaporated to smaller bulk and yielded needles, m. p. 179—181°, of NN′-*bis*-[p-(*di*-2-*ethoxycarbonyl*-2-*formamidoethyl*)-*phenyl*]*thiourea* (III) (1·40 g.). Recrystallisation from ethanol rendered the product colourless and raised the m. p. to 182—183° (Found: C, 56·8; H, 6·0; N, 8·4; S, 4·9. $C_{31}H_{38}O_{10}N_4S$ requires C, 56·5; H, 5·8; N, 8·5; S, 4·9%).

Reaction between Diethyl p-*Aminobenzylformamidomalonate and Diethyl Formamido*-p-iso*thiocyanatobenzylmalonate*.—The amine (31 mg.) and the *iso*thiocyanato-compound (see below) (35 mg., 1·0 mol.) were refluxed for 1 hr. in ethanol (1·5 ml.). The cooled solution deposited colourless needles (35 mg.), m. p. 181·5—182·5°, undepressed on admixture with the disubstituted thiourea (III).

Diethyl Formamido-p-iso*thiocyanatobenzylmalonate* (II*f*; R = H).—The above triethyl-

ammonium dithiocarbamate (0·88 g.), dissolved in dry dioxan (7 ml.), was cooled somewhat in ice-water. Ethyl chloroformate (0·215 g.; 0·19 ml.; 1·10 mol.) was added with shaking, the mixture was kept at room temperature for 30 min., then filtered from the crystalline triethylamine hydrochloride, and the filtrate was evaporated under reduced pressure. Recrystallisation of the colourless crystalline residue from pentanol gave prisms of the iso*thiocyanato*-compound, m. p. 142° (73%) (Found: C, 55·1; H, 5·2; N, 7·9; S, 8·7. $C_{16}H_{18}O_5N_2S$ requires C, 54·85; H, 5·2; N, 8·0; S, 9·0%).

N-p-(*Di-2-ethoxycarbonyl-2-formamidoethyl*)*phenyl-N'-phenylthiourea*.—The above *iso*thiocyanate (63 mg.) and aniline (19 mg., 1·1 mol.) were warmed over a small flame for about a minute. The mixture solidified to a white mass on cooling slightly. Crystallisation from ethanol gave colourless needles of the *thiourea* derivative, m. p. 174° (Found: C, 59·4; H, 5·8; S, 7·0. $C_{22}H_{25}O_5N_3S$ requires C, 59·6; H, 5·7; S, 7·2%).

We thank Mr. J. M. Johnson for technical assistance and Mr. F. H. Oliver, Microanalytical Laboratory, Organic Chemistry Department, Imperial College of Science and Technology, for the analyses. We are also grateful to Roche Products Ltd. for a gift of sodium dithioformate. This investigation has been supported by grants to the Royal Cancer Hospital and Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, March 12th,* 1954.]

The Rearrangement of Some N-*Substituted Hydrazobenzenes.*

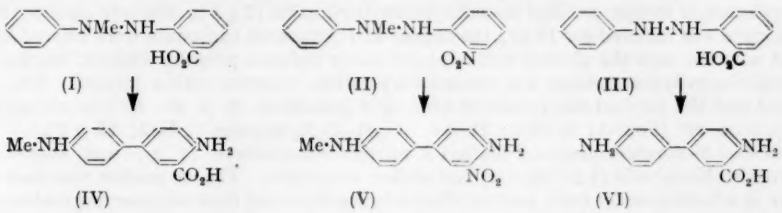
By G. R. CLEMO and T. B. LEE.

[Reprint Order No. 5224.]

Some unsymmetrical *N*-substituted hydrazobenzenes have been prepared and their rearrangements studied.

ALTHOUGH the benzidine transformation has been extensively studied, particularly in the early days by Jacobsen, it is curious to find that the transformation of hydrazobenzenes of the type Ar·NMe·NHAr' (Ar ≠ Ar') has not been investigated. Such hydrazobenzenes were prepared by condensing *as*-methylphenylhydrazine with the corresponding *o*-bromobenzenes and copper powder as a catalyst. In the preparation of *N'*-methylhydrazobenzene-2-carboxylic acid (I) an inert atmosphere is needed or the product is almost exclusively azobenzene-2-carboxylic acid. This easy demethylation of the *N*-methyl group is surprising. If phenylhydrazine itself is used in the condensation in the presence of air azobenzene-2-carboxylic acid is again formed. In the condensation of methylphenylhydrazine and *o*-bromonitrobenzene *N*-methyl-2'-nitrohydrazobenzene (II) is obtained even in the presence of air.

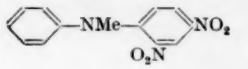
The rearrangements of the hydrazobenzenes (I), (II), and (III) to the benzidines (IV), (V), and (VI) were effected by means of warm dilute hydrochloric acid.



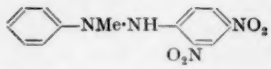
When the amino-acid (IV) was basified with sodium hydroxide the sparingly soluble sodium salt was formed, from which the free acid was isolated by acetic acid. The *N*-

methyl-3′-nitrobenzidine (V) easily forms a monohydrochloride and on reduction the corresponding diamine. This forms a benziminazole with formic acid and a quinoxaline with benzil.

When 1-chloro-2 : 4-dinitrobenzene is used instead of the mononitro-compound *N*-methyl-2 : 4-dinitrodiphenylamine (VII) is obtained. If, however, this condensation is carried out in the absence of copper but with potassium acetate, a mixture of this product (VII) and *N*-methyl-2′ : 4′-dinitrohydrazobenzene (VIII) is obtained. The latter does not rearrange under conditions which convert (I) into (IV).



(VII)



(VIII)

Experimental

N′-*Methylhydrazobenzene-2-carboxylic acid*.—Freshly distilled *as*-methylphenylhydrazine (2 g.), freshly precipitated copper (2 g.), and fused potassium carbonate (2 g.) in absolute alcohol (10 c.c.) were placed in a flask, flushed with nitrogen, a solution of *o*-bromobenzoic acid (2 g.) in absolute alcohol (10 c.c.) was run in, and the mixture refluxed with stirring for 4 hr. in a nitrogen atmosphere. After removal of the alcohol the residue was extracted with water, the copper filtered off, the filtrate carefully neutralised (dilute acetic acid), and the *hydrazobenzene* which was precipitated as a yellow solid was filtered off and recrystallised as soon as possible from methanol–water, giving pale yellow needles (1·4 g.), m. p. 157—158° (Found: C, 69·3; H, 6·0. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

Azobenzene-2-carboxylic Acid.—By the same method and from reactants in air, the brown azo-compound was obtained on addition of dilute acetic acid. This crystallised from light petroleum (b. p. 60—80°) in orange crystals, m. p. 90° (Found: C, 69·0; H, 4·6. Calc. for $C_{13}H_{10}O_2N_2$: C, 69·0; H, 4·4%).

Hydrazobenzene-2-carboxylic Acid.—Freshly distilled phenylhydrazine (2 g.), in place of the *N*-methylphenylhydrazine, gave hydrazobenzene-2-carboxylic acid, which crystallised from ethanol–water in white needles (1·6 g.), m. p. 166—168° (Found: C, 68·5; H, 5·4; N, 12·4. Calc. for $C_{13}H_{12}O_2N_2$: C, 68·4; H, 5·3; N, 12·3%).

N′-*Methylbenzidine-3-carboxylic Acid* (IV).—*N*-Methylhydrazobenzene-2′-carboxylic acid (1 g.) was shaken in dilute hydrochloric acid (50 c.c.; 1 : 4) overnight. The suspension was heated for 1 hr. in a boiling-water bath, then basified with sodium carbonate, and the sodium salt, which is fairly insoluble in water, was filtered off and recrystallised from water. The free *acid* was liberated by suspending the salt in water, adding a few drops of glacial acetic acid, till the solution was almost neutral to litmus, and recrystallising the precipitate from methanol–water (yield, 0·8 g.; m. p. 202—204°) (Found: C, 69·6; H, 6·0. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

Benzidine-3-carboxylic Acid.—Hydrazobenzene-2-carboxylic acid (2 g.) was suspended in dilute hydrochloric acid (1 : 4; 70 c.c.), left overnight, and heated for 1 hr. in a boiling-water bath. The filtered solution was then basified, basic impurities were removed by extraction with ether and the aqueous solution was acidified with dilute acetic acid. The white benzidine-3-carboxylic acid was centrifuged off, the supernatant liquid decanted, and the benzidine purified by dissolution in 3N-hydrochloric acid (charcoal) and precipitation as a white micro-crystalline solid by the addition of excess of sodium acetate (yield, 1 g.; m. p. 209—211°) (Found: N, 12·5. Calc. for $C_{13}H_{12}O_2N_2$: N, 12·3%).

N-*Methyl-2′-nitrohydrazobenzene*.—To a solution of *o*-bromonitrobenzene (10 g.) in absolute alcohol (30 c.c.) were added freshly precipitated copper (1 g.), fused potassium carbonate (4 g.), and a solution of freshly distilled *as*-methylphenylhydrazine (7 g.) in absolute alcohol (20 c.c.). The mixture was refluxed for 13 hr., the copper and potassium carbonate were filtered off from the hot solution, and the alcohol was removed under reduced pressure without heating. The N-*methyl-2′-nitrohydrazobenzene* was obtained crystalline, together with a dark oil. The oil was decanted and the product recrystallised from light petroleum (b. p. 60—80°) as orange prisms (4·7 g.), m. p. 90° (Found: C, 64·3; H, 5·4. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·7%).

N-*Methyl-3′-nitrobenzidine*.—*N*-Methyl-2′-nitrohydrazobenzene (1 g.) was suspended in dilute hydrochloric acid (1 : 1, 25 c.c.) and shaken overnight. The suspension was then heated for 1 hr. in a boiling-water bath, and the clear solution decanted from oily starting material. On cooling, a yellow hydrochloride crystallised and was filtered off and the free base liberated (sodium carbonate) and recrystallised from methanol in purple needles (0·4 g.), m. p. 180—181° (Found: C, 64·2; H, 5·7. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4%). The yellow *monohydro-*

chloride, crystallised from methanol, had m. p. 217—220° (Found: C, 56·4; H, 5·3. $C_{13}H_{13}O_2N_3$,HCl requires C, 55·8; H, 5·0%).

3′-*Amino*-N-*methylbenzidine*.—*N*-Methyl-3′-nitrobenzidine (0·1 g.) in glacial acetic acid (50 c.c.) was hydrogenated at room temperature and pressure over palladium charcoal, 1·06 mols. of hydrogen being absorbed in 1 hr. The catalyst was filtered off and the acetic acid was removed under reduced pressure. The residue was basified (10% aqueous sodium hydroxide) and extracted with ether, the ethereal extract dried (Na_2SO_4), and the ether removed. The diamine was left as a dark red unstable oil which could not be crystallised. It gave a *hydrochloride* which crystallised from concentrated hydrochloric acid in white needles, m. p. 177—180° after sintering at 160° (Found: C, 49·1; H, 5·9. $C_{13}H_{15}N_3$,3HCl requires C, 48·6; H, 5·3%).

2 : 3-*Diphenyl*-6-p-*toluidinoquinoxaline*.—To a solution of 3′-amino-*N*-methylbenzidine (0·2 g.) in absolute alcohol (2 c.c.) was added a hot solution of benzil (0·2 g.) in glacial acetic acid (2 c.c.). The yellow crystalline condensation product, crystallised from ethanol, had m. p. 196—198° (Found: C, 83·7; H, 6·0; N, 11·2. $C_{27}H_{21}N_3$ requires C, 83·7; H, 5·4; N, 10·9%). The *acetyl* derivative had m. p. 215—217° (from alcohol) (Found: C, 80·8; H, 5·7. $C_{29}H_{23}ON_3$ requires C, 81·1; H, 5·4%).

5-N-*Formyl*-p-*toluidinobenziminazole*.—3′-Amino-*N*-methylbenzidine (0·5 g.) was refluxed with anhydrous formic acid (10 c.c.) for 5 hr. Excess of formic acid and the water formed were removed under reduced pressure, and the white solid residue was dissolved in hot dilute acetic acid (charcoal) and then filtered. The *benziminazole* was precipitated on basification (10% sodium hydroxide) and crystallised from methanol–water. It had m. p. 230—232° (Found: C, 71·7; H, 5·7. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2%). The yellow *picrate* had m. p. 276—279° (Found: C, 52·7; H, 3·6. $C_{15}H_{13}ON_3$,$C_6H_3O_7N_3$ requires C, 52·5; H, 3·3%).

N-*Methyl*-2′ : 4′-*dinitrohydrazobenzene*.—(*a*) To a mixture of pure *as*-methylphenylhydrazine (0·5 g.), freshly precipitated copper (0·5 g.), and fused potassium carbonate (0·5 g.) in absolute alcohol (5 c.c.), was added a solution of 1-chloro-2 : 4-dinitrobenzene (1·5 g.) in absolute alcohol (10 c.c.), and the mixture was refluxed for 18 hr. The copper and alcohol were removed. The residue was extracted with hot alcohol and the extract was treated with charcoal; on filtration and cooling, *N*-methyl-2 : 4-dinitrodiphenylamine separated in red needles, m. p. and mixed m. p. 166—167° (Found: C, 57·2; H, 4·0; N, 15·6. Calc. for $C_{13}H_{11}O_4N_3$: C, 57·1; H, 4·1; N, 15·4%).

(*b*) To a solution of 1-chloro-2 : 4-dinitrobenzene (3·2 g.) and sodium acetate (2 g.) in absolute alcohol (30 c.c.) and water (3 c.c.) was added pure *as*-methylphenylhydrazine (2 g.) in absolute alcohol (10 c.c.). The mixture was refluxed for 6 hr., then cooled, and the product was filtered off and fractionally crystallised from alcohol. The *N*-methyl-2′ : 4′-dinitrohydrazobenzene, recrystallised in dark red plates, had m. p. 121—123° (Found: C, 54·0; H, 4·6; N, 19·8. $C_{13}H_{12}O_4N_4$ requires C, 54·2; H, 4·2; N, 19·5%). *N*-Methyl-2 : 4-dinitrodiphenylamine recrystallised in orange needles, m. p. 166—167°.

One of us (T. B. L.) thanks the D.S.I.R. for a Maintenance Grant.

KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, March 20th*, 1954.]

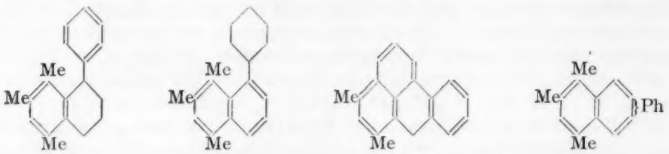
*The Elimination of Non-angular Alkyl Groups in Aromatisation Reactions. Part III.**

By Wesley Cocker and D. S. Jenkinson.

[Reprint Order No. 5232.]

The dehydrogenation of the compounds (I) and (II) is described.

When 1 : 2 : 3 : 4-tetrahydro-5 : 7 : 8-trimethyl-1-phenylnaphthalene (I) was dehydrogenated with selenium under conditions previously described * it gave a mixture from which 2 : 4-dimethyl*meso*benzanthrene (III) was isolated. Light-absorption measurements however suggest that the mixture also contained 1 : 2 : 4-trimethyl-7(or 6)-phenylnaphthalene (IV). The latter compound and its 8-isomer (V) were obtained when (I) was dehydrogenated with palladised charcoal. No evidence was found to indicate that phenyl was lost in any of the reactions mentioned. By contrast, however, when 8-*cyclo*hexyl-1 : 2 : 4-trimethylnaphthalene (II) was heated with selenium 1 : 2 : 4-trimethylnaphthalene was obtained.



(I) (II) (III) (IV)

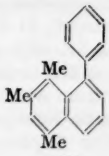
The trimethylphenylnaphthalenes were identified by comparison of their light-absorption spectra with those of 1- and 2-phenylnaphthalenes (cf. Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199). There is close resemblance between the spectra of 2-phenylnaphthalene and (IV), but there is a somewhat greater difference between those of 1-phenylnaphthalene and (V). This is to be expected since there is appreciable hindrance to planarity in (V). In this connection it should be mentioned that neither of the compounds (IV and V) gave stable adducts with picric acid, styphnic acid, or trinitrobenzene, although each gave a highly coloured solution with these reagents. 1-Phenylnaphthalene similarly fails to give adducts; the more planar benzanthrene (III) readily gives a stable adduct with trinitrobenzene. 2-Phenylnaphthalene gives an adduct only with trinitrobenzene.

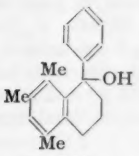
Spectral evidence does not distinguish between 1 : 2 : 4-trimethyl-6- and -7-phenylnaphthalene; (IV) may be either of these.

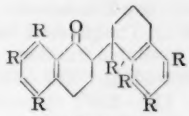
In an attempted preparation of (I), phenylmagnesium bromide was caused to react with 1 : 2 : 3 : 4-tetrahydro-5 : 7 : 8-trimethyl-1-oxonaphthalene (Cocker, Cross, and McCormick, *J.*, 1952, 72). The product was not the expected alcohol (VI) or its dehydration product. In fact the same product was obtained when *cyclo*hexylmagnesium bromide was treated with the tetralone. Although the product fails to give any reactions of a ketone its light absorption is so similar to that of the ketone (VII; R = R′ = H) (cf. Friedel and Orchin, " Ultra-Violet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, 1951, p. 136) that we feel justified in assigning the structure (VII; R = Me, R′ = OH) to the new compound. Steric effects are no doubt responsible for the absence of ketonic properties (cf. Cagniant and Buu-Hoï, *Bull. Soc. chim.*, 1942, **9**, 841; Cocker *et al.*, *J.*, 1950, 1781). Vigorous reduction of this compound over Raney nickel in an autoclave gave 1 : 2 : 3 : 4-tetrahydro-5 : 7 : 8-trimethylnaphthalene. Cook and Lawrence (*J.*, 1936, 1431) obtained a compound presumed to be 1 : 2 : 3 : 4-tetrahydro-1-oxo-2-1′-tetralylidenenaphthalene (IX) from tetralone and *cyclo*hexylmagnesium chloride. When (VII; R = Me, R′ = OH) was heated alone at 150° or with acetic anhydride, the product was 1 : 2 : 3 : 4-tetrahydro-5 : 7 : 8-trimethyl-1-oxonaphthalene, produced no doubt by a reversed aldol

* Parts I and II, *J.*, 1952, 72; 1953, 2355.

condensation. In contrast to the compound (IX) obtained by Cook and Lawrence (*loc. cit.*) neither of the two anhydro-compounds (VIII) can be set up in Courtauld models. It is not


(V)

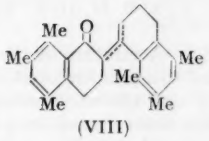

(VI)

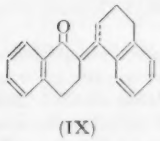

(VII)

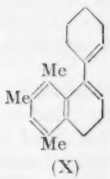
suprising therefore that dehydration of (VII; R = Me, R′ = OH) is impossible. Its reduction to 1 : 2 : 3 : 4-tetrahydro-5 : 7 : 8-trimethylnaphthalene probably proceeds *via* the tetralone. It is relevant that models show that the tetralylidene compound (IX) is much more strained than the corresponding dihydronaphthyl compound indicated in (IX) by the broken line.

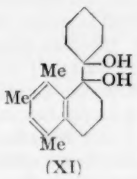
Phenyl-lithium readily reacted with the trimethyltetralone to give the alcohol (VI); this was dehydrated with potassium hydrogen sulphate, and the product reduced, affording (I) in good yield.

8-*cyclo*Hexyl-1 : 2 : 4-trimethylnaphthalene could not be prepared by the method used for the phenyl analogue since it was found impossible to obtain *cyclo*hexyl-lithium (cf. Gilman, Zoellner, and Selby, *J. Amer. Chem. Soc.*, 1933, **55**, 1252). When however a mixture of 1 : 2 : 3 : 4-tetrahydro-5 : 7 : 8-trimethyl-1-oxonaphthalene and *cyclo*hexanone was reduced with aluminium amalgam and the product dehydrated the dihydronaphthalene (X) was obtained. The mixed pinacol (XI) was presumably the intermediate, but this was not isolated. The formation of this pinacol agrees with Wieman's experience (*Compt. rend.*, 1941, **212**, 1032) that it was the main product of the reduction of a mixture of *cyclo*hexanone and ethyl methyl ketone. We were unable to reduce the compound (X): Cook and Lawrence (*loc. cit.*) found that 1-*cyclo*hex-1′-enylnaphthalene showed resistance to reduction. When however (X) was heated under pressure with hydrogen and Raney nickel, isomeric change occurred and a further hydrocarbon was produced, which presented a


(VIII)


(IX)


(X)


(XI)

single absorption maximum (2800 Å; log ε 3·90). Several structures could be assigned to this compound but in view of its properties (II) is the only reasonable one, and the light absorption can best be explained on steric grounds. Models show that (II) is under strain and lacks planarity.

Experimental

Light absorption measurements were made in EtOH.

1 : 2 : 3 : 4-*Tetrahydro*-1-*hydroxy*-5 : 7 : 8-*trimethyl*-1-*phenylnaphthalene* (VI).—Lithium (8 g.) was treated with bromobenzene (7·9 g.) in ether (100 c.c.), under nitrogen. 1 : 2 : 3 : 4-Tetrahydro-5 : 7 : 8-trimethyl-1-oxonaphthalene (6 g.) in ether (50 c.c.) was added, and the mixture was left overnight and then refluxed for 20 min. The product was decomposed with ice and hydrochloric acid, the ether solution was washed with sodium hydroxide, and the dried ethereal extract evaporated to yield the *alcohol* (9·4 g.), m. p. 83—84° (rhombs from ethyl acetate–light petroleum) (Found: C, 85·7; H, 8·2. $C_{19}H_{22}O$ requires C, 85·7; H, 8·3%).

1 : 2-*Dihydro*-5 : 6 : 8-*trimethyl*-4-*phenylnaphthalene*.—The preceding compound (8·5 g.) was heated with freshly fused potassium hydrogen sulphate (20 g.) for 3 hr. at 155°, yielding the

dihydro-compound (4·7 g.), m. p. 89° (needles from alcohol) (Found: C, 91·5; H, 8·2. $C_{19}H_{20}$ requires C, 91·9; H, 8·1%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 7 : 8-*trimethyl*-1-*phenylnaphthalene* (I).—The dihydro-compound (6 g.), reduced in ethyl acetate over Adams catalyst, gave the *tetrahydro*-compound (4·3 g.), m. p. 63° (needles from alcohol) (Found: C, 90·9; H, 9·0. $C_{19}H_{22}$ requires C, 91·2; H, 8·8%).

Dehydrogenation. (*a*) The tetralin (1·5 g.) was heated for 4·5 hr. with palladised charcoal (1·5 g.) at 260—280°. The product was extracted with benzene and then treated with alcohol (15 c.c.), giving an insoluble fraction (A) (0·23 g.) and a solution from which a yellow solid (B) (0·3 g.) separated on cooling. The solid (B) crystallised from benzene–light petroleum as colourless needles, m. p. 133—134°, consisting of 1 : 2 : 4-*trimethyl*-7(or 6)-*phenylnaphthalene* (IV) (Found: C, 92·5; H, 7·3. $C_{19}H_{18}$ requires C, 92·7; H, 7·3%). Light absorption: Max. at 2170, 2590, 2950 Å (log ε 4·51, 4·74, 3·91). Friedel, Orchin, and Reggel (*loc. cit.*) give 2120, 2500, 2850 Å (log ε 4·6, 4·7, 4·05) for 2-phenylnaphthalene.

Distillation of the mother-liquors from (IV) gave 1 : 2 : 4-*trimethyl*-8-*phenylnaphthalene* (V) (0·65 g.), b. p. 189—193°/4 mm., m. p. 77—78° (plates from light petroleum) (Found: C, 92·6; H, 7·2%). Light absorption: Max. at 2370, 3060 Å (log ε 4·65, 4·01). Friedel *et al.* (*loc. cit.*) give 2250, 2880 Å (log ε 4·75, 3·95) for 1-phenylnaphthalene.

Fraction (A) was chromatographed on alumina from benzene–light petroleum, yielding (V) (0·07 g.) and an unidentified solid (0·1 g.), m. p. 270°, which could not be crystallised but gave a brilliant green fluorescent solution in benzene.

(*b*) The tetralin (1·8 g.), dehydrogenated in the usual way with selenium, gave 2 : 4-*dimethyl*-meso*benzanthrene* (III) (0·65 g.), b. p. 200—210°/4 mm., m. p. 82—83° (plates from alcohol) (Found: C, 91·6; H, 7·4. $C_{19}H_{16}$ requires C, 93·4; H, 6·6%). Light absorption: Max. at 2340, 2500, 3350, 3530 Å (log ε 4·54, 4·25, 4·08, 4·03). Clar and Furneri (*Ber.*, 1932, **65**, 1421) give 2280, 2500, 3120, 3290, 3440 Å (log ε 4·65, 4·20, 4·09, 4·24, 4·13) for benzanthrene. It is rapidly oxidised in air, hence the poor analyses. The *trinitrobenzene* adduct (scarlet needles from benzene–light petroleum) had m. p. 136° (Found: C, 66·0; H, 4·7. $C_{25}H_{19}O_6N_3$ requires C, 65·6; H, 4·2%).

Action of cyclo*Hexyl- and Phenyl-magnesium bromide on* 1 : 2 : 3 : 4-*Tetrahydro*-5 : 7 : 8-*trimethyl*-1-*oxonaphthalene*.—The tetralone (6·3 g.) in ether (50 c.c.) was added to a solution from magnesium (0·83 g.) and *cyclo*hexyl bromide (5·5 g.) or bromobenzene (5·2 g.) in ether (50 c.c.). The mixture was decomposed next morning in the usual way, yielding a solid (3·5 g.), m. p. 152—153° (prisms from chloroform–light petroleum) (Found: C, 82·3; H, 8·3. $C_{26}H_{32}O_2$ requires C, 83·0; H, 8·5%). Light absorption: Max. at 2640 and 3160 Å (log ε 4·12, 3·39).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 7 : 8-*trimethyl*-1-*naphthol*.—The corresponding tetralone (1·0 g.) was reduced in ether (110 c.c.) with lithium aluminium hydride (1 g.), yielding the *tetralol* (1 g.), m. p. 78° (needles from light petroleum–methyl alcohol) (Found: C, 81·9, H, 10·0. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

1 : 2-*Dihydro*-4-cyclo*hex*-1′-*enyl*-5 : 7 : 8-*trimethylnaphthalene* (X).—A mixture of the tetralone (9·4 g.), *cyclo*hexanone (5 g.), and dry benzene (40 c.c.) was added to a mixture of aluminium foil (8 g.), dry benzene (100 c.c.), and anhydrous alcohol (200 c.c.), and the whole refluxed for 2 hr. Anhydrous alcohol (100 c.c.) was then added and the mixture was refluxed for a further 6 hr. The suspension was added to dilute hydrochloric acid, the organic layer separated, and the aqueous layer was extracted with benzene. From the combined organic extracts an oil was obtained which was refluxed for 2 hr. with acetic acid (50 c.c.) and acetic anhydride (50 c.c.). On cooling, the required *dihydronaphthalene* separated as needles (3·2 g.) and was further crystallised from acetic acid. It had m. p. 217° (rapid heating) (Found: C, 90·5; H, 8·8. $C_{19}H_{24}$ requires C, 90·5; H, 9·5%). Light absorption: no maxima, the absorption falling in uniform manner from 2120 to 3100 Å with inflexion at 2600 Å. The low solubility in suitable solvents made quantitative measurement of absorption impossible. The compound gave a deep permanganate colour with concentrated sulphuric acid and rapidly decolorised permanganate.

8-cyclo*Hexyl*-1 : 2 : 4-*trimethylnaphthalene* (II).—The preceding compound (3 g.) in alcohol (150 g.) was heated in hydrogen with Raney nickel (1 g.) for 6 hr. at 150°/100 atm. The *naphthalene* crystallised from benzene–light petroleum as needles (2·4 g.), m. p. 158—159° (Found: C, 90·5; H, 9·3. $C_{19}H_{24}$ requires C, 90·5; H, 9·5%). Light absorption: Max. at 2800 Å (log ε 3·90). It failed to give a picrate, but gave a scarlet colour with concentrated sulphuric acid. It decolorised permanganate only very slowly.

Dehydrogenation.—The naphthalene (1·4 g.), heated with selenium under the usual conditions, gave a product which on distillation gave two fractions, (A) (0·45 g.) b. p. 150—153°/14 mm., and (B) (0·4 g.) b. p. 180—210°/16 mm. The former crystallised from methyl alcohol as plates, m. p.

and mixed m. p. with authentic 1 : 2 : 4-trimethylnaphthalene 52—53°. Its picrate, m. p. 146—147°, was undepressed on admixture with that of 1 : 2 : 4-trimethylnaphthalene (cf. Ruzicka and Ehmann, *Helv. Chim. Acta*, 1932, **15**, 140). Attempts to purify fraction (B) were unsuccessful. It did not give a picrate.

The authors thank the Government of Northern Ireland and the Medical Research Council of Ireland for grants, and Imperial Chemical Industries Limited for gifts of materials.

UNIVERSITY CHEMICAL LABORATORY, TRINITY COLLEGE, DUBLIN. [*Received, March 23rd*, 1954.]

Hydrazine. Part VIII. Some Salts of* 3 : 5 : 5-*Trimethyl*-Δ^2-*pyrazoline and of* 3 : 5 : 5-*Trimethyl*-1-iso*propylidene*-Δ^2-*pyrazolinium Ion.*

By W. PUGH.

(*With Notes on the Optical Properties of the Crystals.* By H. C. G. VINCENT.)

[Reprint Order No. 5002.]

Salts of 3 : 5 : 5-trimethylpyrazoline are shown to condense with acetone, in acidic media, forming salts of a new ion which contain the *iso*propylidene radical attached to the pyrazoline ring. It is suggested that condensation occurs at the site of the positively charged nitrogen atom. Chloro-, bromo-, and iodo-stannates, -platinates, -antimonites, and -bismuthites of both 3 : 5 : 5-trimethylpyrazoline and 3 : 5 : 5-trimethyl-1-*iso*propylidene-pyrazolinium ion are described and characterised.

PARTS I, II, IV, and VI of this series have described a variety of salts of some new bases, *viz.*, ketazines and hydrazones, obtained by crystallisation of mixed halides of certain metals and hydrazine from ketone–water mixtures. The chlorostannate, the first salt described, was originally reported as a hydrazinium salt containing acetone of crystallisation, but, for reasons set out in Part VI (*loc. cit.*), it was later re-formulated as the salt of dimethyl ketazine.

Parts I and II (*locc. cit.*) also described a chlorostannate of 3 : 5 : 5-trimethylpyrazoline containing 2 mols. of acetone of crystallisation, and now, in view of the revised formulation of the hydrazinium salt (above), it has become necessary to re-examine the mode of attachment of acetone in this and in many other similar salts containing 3 : 5 : 5-trimethylpyrazoline now described.

These salts are now also shown to contain a new type of cation, a product of condensation of acetone with the 3 : 5 : 5-trimethylpyrazolinium ion. The reasons for this revised view are: (1) The acetone in these, as in the ketazinium salts, though readily removable by hydrolysis in aqueous media, is not removable by heating (the dry salts can be heated *in vacuo* to 110° without loss in weight). (2) The acetone recoverable by hydrolysis is, in every salt so far made, exactly 1 mole per mole of 3 : 5 : 5-trimethylpyrazoline present (thus, salts containing univalent anions, *e.g.*, chloroantimonites, yield 1 mole of acetone, and salts containing bivalent anions, *e.g.*, chloroplatinates, yield 2 moles of acetone per " mole " of salt—this strict stoicheiometry would be most fortuitous if the acetone were not condensed, mole for mole). (3) The analytical results for the original salt (the chlorostannate) being somewhat inconclusive at the time because the authors were then uncertain of the reliability of carbon and hydrogen values obtainable for compounds containing volatile metal halides, have now been shown, by extended experience in the analysis of ketazinium and hydrazonium salts containing tin, antimony, and bismuth halides, to have been reliable enough to indicate the complete absence of oxygen. Moreover, the estimated percentages of metal and halogen in this and other similar salts described below agree better with a formulation which implies condensation with elimin-

* Parts I, II, IV, VI, VII, *J.*, 1952, 4138; 1953, 354, 2491, 3445; 1954, 1385.

ation of water. (4) The infra-red spectrum of the chlorostannate shows no indication of a band characteristic of the acetone carbonyl group (personal communication from Dr. P. C. Carman).

These facts then suggest very strongly that acetone is not present in these compounds as an adduct, and, in considering the actual site of condensation, it is suggested that, by analogy with hydrazine which condenses to the ketazinium ion (Part VI), 3 : 5 : 5-trimethylpyrazoline reacts with acetone in acid solution to form the 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium ion. It is realised that this is not the only possible site, but a large body of experimental evidence will be presented in Part IX (following paper) to show that this is the position where condensation occurs in the compounds herein described.

The present paper describes some new salts of 3 : 5 : 5-trimethylpyrazoline (chloro-, bromo- and iodo-stannates, -platinates, -antimonites, and -bismuthites) and corresponding salts containing the condensed ion. The two series of salts are readily interconvertible; condensation of acetone and 3 : 5 : 5-trimethylpyrazoline salts occurs with the greatest facility in acid solution, and the salts of 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium ion crystallise from aqueous acetone or from methanol–acetone solution; on the other hand, these salts lose acetone on long standing in, or on evaporation with, acids, and yield salts of 3 : 5 : 5-trimethylpyrazoline. If the acid ion is stable (chloro- and bromo-platinates) the salts give clear solutions in water, but tin, antimony, and bismuth complex salts are decomposed on dilution with water, yielding insoluble hydrated oxide or basic halide. They are insoluble in light petroleum, benzene, carbon tetrachloride, chloroform, and ether but readily soluble in alcohol and in aqueous acetone. They crystallise well when solutions in acetone–water (approx. 8 : 1) are evaporated slowly in partly covered vessels.

Experimental

The methods of analysis used were those reported in Part VI (*loc. cit.*). As there indicated, combustion analysis of compounds of tin, antimony, and bismuth gives values for carbon and hydrogen which are less reliable than values obtained by standard methods for halogens and metals.

General Method of Preparation.—Except where otherwise stated, salts containing the 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium ion were made by crystallisation, from aqueous acetone, of mixtures of metal halide and 3 : 5 : 5-trimethylpyrazolinium chloride, in the required molar ratios. Concentrated solutions of the mixed salts were usually made in the corresponding acid, the minimum of acid being used to counter the tendency of the metal salts to hydrolyse, and the clear solutions were then poured into 4 or 5 vols. of acetone. The mixtures usually became warm. They were then set aside to evaporate at room temperature, good crystals being obtained by slow evaporation in partly covered vessels.

The salts of 3 : 5 : 5-trimethylpyrazoline were, in some cases, obtained by evaporation of the above salts with the appropriate acid, followed by crystallisation, or by evaporation with alcohol (undried) followed by precipitation with ether; in both processes, acetone is removed by hydrolysis; in other cases, they were made by simple crystallisation of acidified solutions of the mixed halides of metal and 3 : 5 : 5-trimethylpyrazoline; but, being generally very soluble, these salts were more difficult to crystallise from aqueous solution.

Preparation of 3 : 5 : 5-*Trimethylpyrazolinium Chloride.*—This salt has hitherto been prepared from the free base, made from the hydrazine salt of maleic acid and from dimethyl ketazine (Curtius and Forsterling, *Ber.*, 1894, **27**, 771), from mesityl oxide (Curtius and Wirsing, *J. pr. Chem.*, 1894, **50**, 531), and from mesitylnitrimine (Harries, *Annalen*, 1901, **319**, 233). For the work described here it was conveniently made as follows: dry acetone (100 c.c.) was boiled under reflux with hydrazine dihydrochloride (50 g.) until the salt passed completely into solution (3—4 hr.). About 80% of the acetone was then distilled off and the concentrated liquor was seeded. The crude product was washed several times with dry acetone, yielding prisms (30 g.), m. p. 175—176° (lit., 176—177°). Yields were lower when undried acetone was used.

The corresponding bromide was made, for use in the preparation of some of the bromo-salts described, by repeated evaporation of the chloride with hydrobromic acid, but the use of the bromide was later found to be unnecessary, the bromo- and iodo-salts crystallising in the pure

state from solutions containing the chloride if sufficient hydrobromic acid and hydriodic acid, respectively, were present.

Bis-(3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium*) *Hexachlorostannate.*—Acetone (50 c.c.) containing stannic chloride (5 c.c., 0·042 mol.) was boiled under reflux for several hours with hydrazine dihydrochloride (9 g., 0·086 mol.), whereupon the latter passed slowly into solution and the deep red liquor deposited yellowish crystals (20 g.). The crude product contained tin and chlorine in the atomic ratio 1 to 6·0, but it was contaminated with traces of bis(dimethyl ketazinium) hexachlorostannate, as shown by titration with iodate (Andrews's method). It was therefore boiled under reflux with fresh acetone (50 c.c.), whereupon the residue (16 g.; m. p. 215—218°) became colourless. It was identical in composition with a small crop (1 g.), m. p. 217—219° (decomp.), obtained by crystallisation of the acetone liquor [Found: C, 33·5; H, 5·4; N, 8·9; Cl, 33·2; Sn, 18·5; C_3H_6O, 18·3. $(C_9H_{17}N_2)_2SnCl_6$ requires C, 33·8; H, 5·3; N, 8·8; Cl, 33·4; Sn, 18·6; C_3H_6O, 18·2%]. The same salt, *bis-*(3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium*) *hexachlorostannate*, was also obtained by adding acetone to a solution of stannic chloride (0·3 c.c.) and 3 : 5 : 5-trimethylpyrazolinium chloride (0·7 g.) in ethanol (10 c.c.) acidified with hydrochloric acid, the m. p. of this sample being raised to 221° (decomp.) by recrystallisation from methanol–acetone.

The crystals are orthorhombic (or monoclinic elongated parallel to *b*), with an elongated needle habit, and sometimes a rectangular pinacoidal habit, resembling cubes; colourless in sections and without cleavage. $Bx^a(\gamma)$ is parallel to the elongation. Positive. $2V(\gamma) = 30—35°$. Dispersion faint, red > violet. n_D : $\alpha = 1·55$; $\gamma = 1·673$.

The salt is not deliquescent and is stable for long periods in air. It suffers no loss in weight when heated for several hours *in vacuo* at 110° [which is one reason for discarding the original formulation of the salt as a chlorostannate of 3 : 5 : 5-trimethylpyrazoline with acetone of crystallisation; Part I, *loc. cit.*)]. It is insoluble in light petroleum, benzene, carbon tetrachloride, chloroform, and ether; sparingly soluble in ethanol and acetone; and more soluble in mixtures of acetone with alcohol or water. It dissolves in about its own weight of water, but diluted solutions slowly become turbid. Aqueous solutions, and solutions in dilute acids, yield yellow precipitates with 2 : 4-dinitrophenylhydrazine only after several minutes, indicating that acetone is liberated slowly by hydrolysis. Hydrolysis is, however, accelerated by heat, and when the salt is evaporated with hydrochloric acid the resulting solution contains bis-(3 : 5 : 5-trimethylpyrazolinium) hexachlorostannate, described below. Aqueous alkalis also cause hydrolysis, liberating acetone and the free base, 3 : 5 : 5-trimethylpyrazoline, which was recovered by ether extraction and identified.

Bis-(3 : 5 : 5-*trimethylpyrazolinium*) *Hexachlorostannate.*—One method of preparing this salt has already been described (Part I, *loc. cit.*). It has also been made from a sample of bis-(3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium) hexachlorostannate, by evaporation on a water-bath with dilute hydrochloric acid and crystallisation of the concentrated liquid, but it was most readily obtained by crystallisation of mixtures of stannic chloride (1 mol.) and 3 : 5 : 5-trimethylpyrazolinium chloride (2 mols.) from hot dilute hydrochloric acid. It forms needles and prisms, m. p. 198° (decomp.) [Found: C, 25·3; H, 4·8; N, 10·0; Cl, 38·2; Sn, 21·1. Calc. for $(C_6H_{13}N_2)_2SnCl_6$: C, 25·8; H, 4·7; N, 10·0; Cl, 38·2; Sn, 21·3%].

The crystals are biaxial, probably monoclinic, with a pronounced flaky habit and cleavage parallel to (010), and colourless in mounts. Positive. $2V(D) = 31°$. Dispersion imperceptible. n_D : $\alpha = 1·569$, $\gamma = 1·605$, $(\gamma - \alpha) = 0·036$.

Its solubilities resemble those of the preceding salt. Its solutions in alcohol or water, treated with acetone, yield bis-(3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium) hexachlorostannate.

Bis-(3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium*) *Hexabromostannate.*—Tin (2 g., 0·017 g.-atom) was added in small pieces to an excess of well-cooled bromine, and when the metal had dissolved completely the excess of bromine was removed in a current of hot air. Acetone (30 c.c.), hydrobromic acid (48%; 1 c.c.), and hydrazine monohydrobromide (3·8 g., 0·033 mol.) were then added and the solution was boiled under reflux. After 4 hr., the liquid had become reddish and yellow cubes began to separate, but boiling was continued for 10 hr., and there then seemed to be no further increase in yield. The crude product (13 g.) was crushed and heated under reflux with fresh acetone for another hour, the residue (10 g.) consisting of yellow cubes, m. p. 216—218°, identical with a small crop (1 g.), m. p. 217—218° (decomp.), obtained by crystallisation of the acetone extract [Found: C, 24·1; H, 4·0; N, 5·8; Br, 52·9; Sn, 13·0; C_3H_6O, 13·3. $(C_9H_{17}N_2)_2SnBr_6$ requires C, 23·9; H, 3·8; N, 6·2; Br, 53·0; Sn, 13·1; C_3H_6O, 12·8%]. A similar *salt*, m. p. 216—217° (decomp.), was obtained when a methanol solution of bis-(3 : 5 : 5-trimethylpyrazolinium) hexabromostannate, described below, was treated with an

excess of acetone and the mixture set aside for a few hours. The hexabromostannate is similar to the hexachlorostannate in its behaviour towards organic solvents and aqueous acids and alkalis. It is also stable in air and non-deliquescent. The crystals are lemon-yellow cubes, colourless in microscopic mounts. Pseudo-cubic(?); $n_D = 1{\cdot}656$. The crystals are essentially isotropic, but show fine patchy anisotropic lamellæ and cross hatching parallel to the cube faces.

Bis-(3 : 5 : 5-*trimethylpyrazolinium*) *Hexabromostannate.*—A sample of bis-(3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium) hexabromostannate was boiled with a large volume of ethanol, and the resulting solution evaporated to small bulk, cooled, and treated with ether. Yellow crystals separated, m. p. 193° [Found: C, 17·6; H, 3·1; Br, 58·1; Sn, 14·3. $(C_6H_{13}N_2)_2SnBr_6$ requires C, 17·5; H, 3·2; Br, 58·2; Sn, 14·4%]. The *salt* was also made by adding ether to a solution of stannic bromide and 3 : 5 : 5-trimethylpyrazolinium bromide in ethanol. The crystals are biaxial, in anhedral grains without cleavage, and colourless in mounts. Positive. $2V(D) = 80$—85° (estimated). Dispersion is very strong, red > violet, giving anomalous interference colours. n_D: $a = 1{\cdot}651$, $\gamma = 1{\cdot}660$, $(\gamma - \alpha) = 0{\cdot}009$.

Bis-(3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium*) *Hexachloroplatinate.*—This *salt* was made by the general method (see above) from chloroplatinic acid hexahydrate (2·6 g.), 3 : 5 : 5-trimethylpyrazolinium chloride (1·5 g.), and acetone (10 c.c.). The orange-yellow cubes decompose, becoming black, at about 170°, and melt, with rapid decomposition, at about 185°. (Halogen in this, and in the bromoplatinate, described below, was determined by the author's method, *J. Appl. Chem.*, 1954, 47) [Found: C, 29·6; H, 4·6; Cl, 29·9; Pt, 27·3; C_3H_6O, 16·4. $(C_9H_{17}N_2)_2PtCl_6$ requires C, 30·1; H, 4·8; Cl, 29·8; Pt, 27·3; C_3H_6O, 16·2%]. The crystals are probably cubic, or pseudo-cubic, the cubes being often modified by small faces of the (110) and other forms. Symmetry appears to be cubic. Cleavage is absent, and the crystals are light yellowish-brown in mounts. They show distinct but low birefringence, in patches and irregular areas which cannot be resolved, giving rise to undulose extinction; they give no decipherable convergent light figure. $n_D = 1{\cdot}646$ (approx.).

Bis-(3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium*) *Hexabromoplatinate.*—Chloroplatinic acid hexahydrate (2·6 g.) and 3 : 5 : 5-trimethylpyrazolinium chloride (1·5 g.) were evaporated separately and repeatedly with hydrobromic acid and the resulting syrups were taken up in acetone and mixed. The dark liquid yielded dark red cubes which blacken at about 200° and melt at 219° with vigorous decomposition [Found: C, 21·7; H, 3·3; Br, 49·0; Pt, 19·9. $(C_9H_{17}N_2)_2PtBr_6$ requires C, 22·0; H, 3·5; Br, 48·9; Pt, 19·9%]. The crystals are probably cubic. They are isotropic, with a simple cubic habit. Cleavage is absent, and the crystals are brownish-red to yellow in mounts, and without pleochroism. $n_D = 1{\cdot}726$.

3 : 5 : 5-*Trimethyl*-1-iso*propylidenepyrazolinium Tetrachloroantimonite.*—The general method of preparation (see p. 2424) was used, and the crude product was recrystallised from acetone acidified with hydrochloric acid. The colourless needles or prisms contained acetone of crystallisation (Found: C, 27·3; H, 4·2; Cl, 32·5; Sb, 27·9; C_3H_6O, 17·4. $3C_9H_{17}N_2SbCl_4,C_3H_6O$ requires C, 27·5; H, 4·4; Cl, 32·6; Sb, 27·9; C_3H_6O, 17·7%). (The acetone determined is the total liberated on hydrolysis.) The *salt* has no sharp m. p., partial melting occurring at 60°, clearing at 80°. (Bubbles of vapour, probably acetone of crystallisation, are emitted within, and above, the melting range.) It loses all its acetone of crystallisation when heated to constant weight at 78°/20 mm. (Found: loss, 5·0. Required: loss, 4·5%), the product being pure 3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium tetrachloroantimonite*, m. p. 84—85° (Found: C, 26·2; H, 4·3; Cl, 34·2; Sb, 29·2. $C_9H_{17}N_2SbCl_4$ requires C, 25·9; H, 4·1; Cl, 34·2; Sb, 29·3%).

3 : 5 : 5-*Trimethylpyrazolinium Tetrachloroantimonite.*—Crystallisation of a solution containing antimony trioxide (3 g.) and 3 : 5 : 5-trimethylpyrazolinium chloride (3 g.) in the minimum of hot, 6N-hydrochloric acid (15 c.c.) yielded large rods or prisms, m. p. 55—56°, of the *hydrate* (Found: C, 17·8; H, 3·6; Cl, 36·1; Sb, 30·8. $C_6H_{13}N_2SbCl_4,H_2O$ requires C, 18·2; H, 3·8; Cl, 36·0; Sb, 30·8%). The crystals are probably monoclinic, being elongated, simply modified, pinacoidal rods, with distinct cleavage parallel to the rods. They are colourless. The extinction angle is about 15°. Positive. $2V(D) = 29°$. Dispersion perceptible, red > violet. n_D: $\alpha = 1{\cdot}595$, $\beta = 1{\cdot}601$, $\gamma = 1{\cdot}688$, $(\gamma - \alpha) = 0{\cdot}093$.

The hydrated salt loses water rapidly at 100° (Found: loss, 4·5. Required: loss, 4·6%) and, in air at 100°, there is a further small loss, probably of hydrogen chloride, by hydrolysis. A sample kept at 100° for 8 hr. in air lost 6·4% in weight, giving the impure anhydrous salt (Found: Cl, 37·2; Sb, 32·8. Calc. for $C_6H_{13}N_2SbCl_4$: Cl, 37·7; Sb, 32·4%).

3 : 5 : 5-*Trimethyl*-1-iso*propylidenepyrazolinium Tetrabromoantimonite.*—This solvated *salt* was made by the general method (see p. 2424) from antimony oxide, hydrobromic acid, 3 : 5 : 5-

trimethylpyrazolinium chloride, and acetone, and was recrystallisated from acetone containing 10% of hydrobromic acid. The yellow plates contained acetone of crystallisation (Found: C, 19·4; H, 3·1; Br, 52·1; Sb, 19·8; C_3H_6O, 12·8. $3C_9H_{17}N_2SbBr_4,C_3H_6O$ requires C, 19·5; H, 3·1; Br, 52·1; Sb, 19·8; C_3H_6O, 12·6%). The crystals are biaxial, poorly developed, equidimensional forms with some tendency to platy habit; they have no cleavage and are colourless in mounts. Orientation uncertain, the salt being unstable in available immersion liquids. Positive. $2V$ about 75°. Dispersion imperceptible. n_D: β, 1·72 (approx.). Birefringence very high.

The salt does not melt sharply; plastic flow occurs at 78°, vapour bubbles being emitted more rapidly as the temperature rises, and the melt clears at 87°. It loses its acetone of crystallisation when heated at 78°/20 mm. (Found: loss, 3·6. Required: loss, 3·1%), yielding 3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium tetrabromoantimonite*, m. p. 94—95° (Found: C, 18·2; H, 2·9; Br, 53·7; Sb, 20·6. $C_9H_{17}N_2SbBr_4$ requires C, 18·2; H, 2·9; Br, 53·7; Sb, 20·5%).

3 : 5 : 5-*Trimethylpyrazolinium Tetrabromoantimonite*.—This *salt* crystallises anhydrous from solutions containing antimony oxide and 3 : 5 : 5-trimethylpyrazolium chloride, in the required proportions, in excess of hydrobromic acid. It separates as large yellow prisms or rods, m. p. 66—67° (Found: C, 12·7; H, 2·6; Br, 57·6; Sb, 21·8. $C_6H_{13}N_2SbBr_4$ requires C, 13·0; H, 2·3; Br, 57·7; Sb, 22·0%). The crystals are probably monoclinic, being stout, simply modified, prismatic and pinacoidal forms, with some tendency to elongation, and without cleavage. Colourless in mounts. The optic axial plane is parallel to the elongation direction and is probably parallel to (010). Oblique extinction of about 10°. Positive. $2V(\gamma) = 46°$. Dispersion marked, red > violet. n_D: $\alpha = 1{\cdot}750$, $\beta = 1{\cdot}763$, $\gamma > 1{\cdot}84$. Birefringence near 0·1.

3 : 5 : 5-*Trimethyl*-1-iso*propylidenepyrazolinium Tetraiodoantimonite*.—This *salt* is less soluble and crystallises more readily than the bromo- and chloro-analogues. It was obtained from a solution containing antimony iodide (1 g.), potassium iodide (0·3 g.), hydriodic acid (0·5 c.c.), 3 : 5 : 5-trimethylpyrazolinium chloride (0·3 g.), and acetone (10 c.c.) and was recrystallised from acetone–water (4 : 1) (Found: C, 14·2; H, 2·1; I, 65·0; Sb, 15·7. $C_9H_{17}N_2SbI_4$ requires C, 13·8; H, 2·2; I, 65·0; Sb, 15·6%). The crystals, m. p. 159°, are orange, orthorhombic (or monoclinic, elongated parallel to *b*), generally in irregular grains, but sometimes showing an elongated and platy habit. Cleavage is absent; reddish-yellow in mounts. $Bx^a(\gamma)$ is parallel to the elongation direction. Positive. $2V(D) = 60—65°$ (estimated). Dispersion faintly perceptible, red > violet. Pleochroism marked, maximum absorption γ (reddish-brown), α (yellow). n_D: $\alpha > 1{\cdot}84$. Birefringence moderate.

3 : 5 : 5-*Trimethyl*-1-iso*propylidenepyrazolinium Tetrachlorobismuthite*.—Large, colourless, crystals of this *salt*, m. p. 156°, were obtained by the general method (Found: C, 21·2; H, 3·4; Cl, 28·2; Bi, 41·6; C_3H_6O, 11·0. $C_9H_{17}N_2BiCl_4$ requires C, 21·4; H, 3·4; Cl, 28·2; Bi, 41·5; C_3H_6O, 11·5%). The crystals are monoclinic, poorly developed, stout, pinacoidal forms with a tendency to elongation and with no pronounced cleavage. The optic axial plane is normal to (010). Positive. $2V(\gamma) = 22°$. Axial dispersion rather marked, red > violet, giving anomalous interference colours and incomplete extinction for Bx^a and optic axis sections. n_D: $\alpha = 1{\cdot}644$, $\beta = 1{\cdot}648$, $\gamma = 1{\cdot}710$, $(\gamma - \alpha) = 0{\cdot}066$.

3 : 5 : 5-*Trimethylpyrazolinium Tetrachlorobismuthite*.—This *salt* is exceedingly soluble and was obtained by slow evaporation, over sulphuric acid, of a solution containing bismuth oxychloride (5·2 g.) and 3 : 5 : 5-trimethylpyrazolinium chloride (3 g.) in concentrated hydrochloric acid (8 c.c.) (Found: C, 15·4; H, 2·8; Cl, 30·7; Bi, 45·1. $C_6H_{13}N_2BiCl_4$ requires C, 15·5; H, 2·8; Cl, 30·6; Bi, 45·0%). The crystals are orthorhombic or monoclinic (elongated parallel to *b*), with flaky, lath-shaped habit. Colourless in mounts. The optic axial plane is parallel to the elongation. Negative. $2V(\alpha)$ large, dispersion perceptible. Length positive. n_D (approx.): $\alpha = 1{\cdot}650$, $\gamma = 1{\cdot}775$, $(\gamma - \alpha) = 0{\cdot}125$.

3 : 5 : 5-*Trimethylpyrazolinium Tetrabromobismuthite*.—Crystallisation, from hydrobromic acid solutions, of mixtures of bismuth bromide and 3 : 5 : 5-trimethylpyrazolinium chloride yielded stout, pinacoidal, yellow crystals of the *monohydrate* (Found: C, 11·0; H, 2·3; Br, 48·6; Bi, 31·6. $C_6H_{13}N_2BiBr_4,H_2O$ requires C, 10·9; H, 2·3; Br, 48·5; Bi, 31·7%). It loses the water of crystallisation slowly and completely at 105°, yielding the anhydrous *salt*, m. p. 170—171° (Found: C, 10·9; H, 2·0; Br, 50·1; Bi, 32·7. $C_5H_{13}N_2BiBr_4$ requires C, 11·2; H, 2·0; Br, 50·0; Bi, 32·6%). The crystals of the monohydrate are monoclinic, stout, modified elongated pinacoidal forms, pale yellow in mounts. Cleavage is distinct, parallel to the elongation. The optic axial plane is perpendicular to (010) and $Bx^a(\gamma)$ is inclined at about 25°

to the elongation direction. Positive. $2V(D) = 50$—$60°$ (estimated). Dispersion is very strong, red < violet, giving anomalous interference colours. n_D: β, slightly greater than 1·8 (the crystals are attacked by immersion liquids). Birefringence high.

3 : 5 : 5-*Trimethyl*-1-iso*propylidenepyrazolium Tetrabromobismuthite*.—Mixtures of bismuth bromide (2 mols.) and 3 : 5 : 5-trimethylpyrazolinium chloride or bromide (1 mol.) (see below), crystallised by the general method, yielded yellow crystals of the above *salt* (solvated) (Found: C, 17·3; H, 2·8; Br, 45·6; Bi, 29·7. $3C_9H_{17}N_2BiBr_4,C_3H_6O$ requires C, 17·1; H, 2·7; Br, 45·6; Bi, 29·8%). The crystals lose acetone slowly in air but rapidly at 78°/20 mm. (Found: loss, 2·7. Required: loss, 2·8%), and when heated in a m. p. tube, they emit bubbles of vapour at about 100°, melt partially at about 130° and finally at 149°. The crystals are biaxial, in anhedral grains, with no cleavage, and colourless in mounts. (The surface of the crystals undergoes decomposition to another substance—loss of acetone.) Positive. $2V(D) = 79°$. Dispersion very strong, red < violet, with anomalous interference colours. n_D: $\alpha = 1·721$, $\beta = 1·760$, γ not determined, because the crystals are attacked by immersion liquids.

The acetone-free *salt*, m. p. 149°, was obtained by heating the above salt at 78°/20 mm. (Found: C, 16·3; H, 2·5; Br, 47·0; Bi, 30·6. $C_9H_{17}N_2BiBr_4$ requires C, 15·8; H, 2·5; Br, 46·9; Bi, 30·6%).

When mixtures containing equimolar proportions of the salts were crystallised from aqueous acetone, the crystals had an entirely different composition. Many preparations were made and, though there were very small variations in composition, determinations of the optical properties of the samples showed them to be identical, the values for Br and Bi suggesting a double *salt* of the above acetone-free salt with 3 : 5 : 5-trimethylpyrazolinium bromide (Found: C, 21·0; H, 3·3; Br, 46·0; Bi, 25·8. $3C_9H_{17}N_2BiBr_4,2C_6H_{13}N_2Br$ requires C, 19·3; H, 3·2; Br, 46·1; Bi, 25·8%). The crystals are monoclinic, in laths and needles, or stout prismatic forms, with domes and pinacoids. They have a conchoidal fracture. Colourless in mounts. The optic axial plane is normal to (010), giving a maximum extinction angle of about 35° to the elongation direction. Negative. $2V(\alpha) = 86°$. Axial dispersion marked, red > violet. n_D: $\alpha = 1·715$, $\beta = 1·736$, $\gamma = 1·771$, $(\gamma - \alpha) = 0·056$.

3 : 5 : 5-*Trimethyl*-1-iso*propylidenepyrazolinium Tetraiodobismuthite*.—The various attempts to prepare this salt also indicate the existence of a double *salt* similar to the above bromo-salt. Mixtures, in equimolecular proportions, of bismuth iodide and 3 : 5 : 5-trimethylpyrazolinium chloride, dissolved in aqueous acetone, with the aid of hydriodic acid and potassium iodide, gave scarlet prisms, m. p. 186—188° (Found: C, 16·0; H, 2·4; I, 57·5; Bi, 20·4. $3C_9H_{17}N_2BiI_4,2C_6H_{13}N_2I$ requires C, 15·2; H, 2·5; I, 57·5; Bi, 20·3%). The crystals are monoclinic or triclinic, with poorly developed faces, occasionally with a platy, diamond-shaped habit. They are deep brownish-red to orange-red in mounts, and have no pronounced cleavage. The optic axial plane, which lies along the longer diagonal of the plates, is nearly perpendicular to their surface, which gives a near centred optic axis figure. Positive. $2V = 80°$ (approx.). Dispersion is weak, red < violet. Pleochroism imperceptible. n_D of α is much above 1·84. Birefringence low.

When an excess of bismuth iodide was used for the preparation (*e.g.*, 2 mols.) dark red crystals of 3 : 5 : 5-*trimethyl*-1-iso*propylidenepyrazolinium tetraiodobismuthite*, without acetone of crystallisation, were obtained, m. p. 171—172° (recrystallised from warm acetone) (Found: C, 12·4; H, 1·8; I, 58·7; Bi, 24·2. $C_9H_{17}N_2BiI_4$ requires C, 12·4; H, 1·9; I, 58·5; Bi, 24·0%). The crystals are monoclinic or triclinic, with a stout and somewhat elongated habit; they have no cleavage and are deep red in mounts. The orientation is uncertain. The optic axial plane is inclined to the elongation direction, giving a maximum extinction angle of 25° (approx.). Positive. $2V(D) = 65°$ (estimated). Dispersion not apparent. Pleochroism distinct; α, orange red; γ, deep red. n_D of α is much above 1·84. Birefringence moderate.

Combustion analyses were by Mr. R. von Holdt, and acetone determinations by Mr. M. C. B. Hotz.

University of Cape Town. [*Received, January 2nd*, 1954.]

Hydrazine. Part IX. Condensation Products of Aldehydes and Ketones with Salts of Some Substituted Δ^2-Pyrazolines and Hydrazines.*

By M. Lamchen, W. Pugh, and A. M. Stephen.

[Reprint Order No. 5178.]

Chlorostannates and some other salts are described containing cations which are condensation products of carbonyl compounds and certain Δ^2-pyrazolines. They are chemically similar to the 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium salts described in Part VIII.* *N*-Substituted pyrazolines do not form condensation products under the same conditions. Methylhydrazine in the presence of acetone and acids yields *N*-methyldimethylketazinium salts. It is concluded that condensation in all these cases occurs at the secondary amino-group. Phenylhydrazine with acids and acetone yields phenylhydrazonium salts, but these isomerise on long boiling, yielding salts of 3 : 5 : 5-trimethyl-1-phenylpyrazoline.

This paper presents the evidence for the suggestion made in Part VIII * that condensation of acetone with 3 : 5 : 5-trimethyl-Δ^2-pyrazoline in the presence of acids leads to the formation of 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium salts. Such condensation is abundantly substantiated by using a number of aldehydes in place of acetone, whereby derivatives of the chlorostannate of 3 : 5 : 5-trimethylpyrazoline are readily prepared which are stable towards heating *in vacuo* but liberate the aldehyde when kept in aqueous acid or alkaline solution. In these derivatives the molar ratio of carbonyl compound to pyrazoline is always unity, and they are clearly of the same type as the salts described in Part VIII.

To determine the position of condensation, other substituted pyrazolinium chlorostannates were treated with acetone and certain aldehydes under similar conditions. Condensation occurred very readily with the chlorostannates of 5-methylpyrazoline and 4 : 5-dimethylpyrazoline, but not at all with the corresponding salts of 1 : 3 : 5 : 5-tetramethylpyrazoline, 3 : 5 : 5-trimethyl-1-phenylpyrazoline, 1 : 5-dimethylpyrazoline, and 1 : 1(?) : 5-trimethylpyrazoline. The revelant common feature of the pyrazoline bases whose salts condense is an unsubstituted secondary amino-grouping at position 1; replacement of hydrogen on this nitrogen atom by methyl or phenyl groups (*i.e.*, conversion into a tertiary amine) inhibits condensation under the mild conditions used. More vigorous treatment might cause condensation elsewhere in the pyrazoline nucleus (see p. 2430).

In the earlier stages of this work the 3-methyl group, activated as it is in 3 : 5 : 5-trimethylpyrazoline and its salts by the $N{:}C_{(3)}$ system, was considered a possible site of condensation. 3-*iso*Butenyl-5 : 5-dimethylpyrazoline was accordingly prepared and converted into a chlorostannate in the presence of acetone: the product, however, was not identical with the chlorostannate of 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazoline but contained an additional *iso*propylidene group attached to the base.

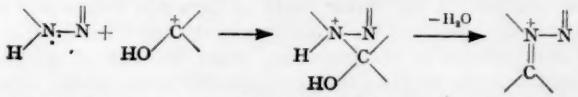
The view that the new cations contain the system (I) is supported by the preparation of the methochloride of cinnamylideneaniline by Zincke and Würker (*Annalen*, 1905, **338**, 133) and of salts of *iso*propylidene or cinnamylidene derivatives of a number of secondary amines (piperidine, diphenylamine, and methylaniline) by ourselves (forthcoming publication), all of which contain a positively charged nitrogen atom linked to three carbon atoms, one of them by a double bond. An even closer analogy is afforded by the condensation of methylhydrazine hydrochloride with acetone in the presence of stannic chloride to give a chlorostannate containing the *N*-methyldimethylketazinium ion; here the cation possesses the same atomic and electronic environment about a positively charged nitrogen atom as is depicted in (I), and it is in fact closely related in structure to the 3 : 5 : 5-trimethyl-1-*iso*propylidenepyrazolinium ion. It is noteworthy that this last experiment yielded an open-chain ion, in contrast to the pyrazolinium ions formed when phenylhydrazine and hydrazine hydrochlorides were used.

$$:N\cdot\overset{+}{N}_{(1)}\cdot C \quad \dot{C} \quad \text{(I)}$$

* Part VIII, preceding paper.

Whereas chlorostannates, chloroplatinates, and other complex salts containing condensed pyrazolinium ions are readily formed, considerable difficulty has been experienced in preparing corresponding chlorides. This may be due to the greater solubility and hygroscopic character of these salts; consequently, the reaction products of 3 : 5 : 5-trimethylpyrazoline hydrochloride and benzaldehyde or acetone have not been isolated pure. The product from cinnamaldehyde has, however, been obtained pure and shown to be readily convertible into the chlorostannate on treatment with alcoholic stannic chloride. Cinnamaldehyde has been found particularly suitable in this work because of its high reactivity and the insolubility of its condensation products. The main drawback is the possibility of its reacting in a different manner from that of aromatic or saturated aliphatic aldehydes, namely, by addition first to the double bond αβ to the carbonyl group. This is known to occur in reactions with piperidine and other secondary amines (Mannich, Handke, and Roth, *Ber.*, 1936, **69**, 2112; Mannich and Davidsen, *ibid.*, p. 2106), but the yellow colour of the compounds formed from pyrazolinium salts and αβ-unsaturated aldehydes (cinnamaldehyde, crotonaldehyde, and tiglic aldehyde) suggests that condensation occurs in these compounds through the aldehyde group to form a conjugated chain involving the pyrazoline double bond.

The reaction of carbonyl compounds with pyrazolinium salts, with or without the addition of excess of acid, is presumably of the normal acid-catalysed type, involving reaction between a carbonium ion and a molecule of the free base; it is unlikely that $N_{(1)}$ would bear a positive charge at the moment of addition. 3 : 5 : 5-Trimethylpyrazoline is a very weak base (K_b approx. 10^{-9}; unpublished work) and small amounts of free base would therefore be present in acid solution. A possible mechanism is as follows :



In processes of alkylation and benzoylation the free pyrazoline bases behave as secondary amines (Curtius and Wirsing, *J. pr. Chem.*, 1894, **50**, 546), and preliminary experiments have shown that if $N_{(1)}$ is unsubstituted, they react with aldehydes, in neutral or alkaline media, to form products in which the base and aldehyde residues are in the molar ratio of 2 to 1 (cf. Mannich and Davidsen, *loc. cit.*). If, on the other hand, the secondary amino-group is benzoylated, no reaction occurs under relatively mild conditions, *e.g.*, when 1-benzoyl-3 : 5 : 5-trimethylpyrazoline is heated for short periods with acetone, benzaldehyde, or cinnamaldehyde. Furthermore, the tertiary amines 1-phenyl- and 5-methyl-1-phenyl-pyrazoline are known to require long heating with benzaldehyde at a high temperature before condensation takes place, not on nitrogen, but at the 4-methylene group (Curtius and Wirsing, *loc. cit.*; Trener, *Monatsh.*, 1900, **21**, 1111). This type of condensation is clearly very different from those described in Part VIII and in this paper.

Experimental

Methods of analysis used were as reported in Parts I and VI (*J.*, 1952, 4138; 1953, 3445). Difficulties with the Volhard estimation of chloride, encountered with the yellow derivatives of cinnamaldehyde, were overcome by decomposing the sample in boiling sodium hydroxide (halogen-free) and extracting the liberated aldehyde and pyrazoline with ether. Chloroplatinates were destroyed with hydrazine before Volhard's method was applied (Pugh, *J. Appl. Chem.*, 1954, **4**, 47). As previously noted in work on ketazinium salts, carbon values are usually a little low, probably owing to surface hydrolysis by moist air.

Reaction of Bis-(3 : 5 : 5-trimethylpyrazolinium) Hexachlorostannate with Carbonyl Compounds.—The above salt, made as described in Part VIII (*loc. cit.*) from a mixture of the simple salts, was treated in ethanolic solution (approx. 30% w/v) with excess of the appropriate aldehyde or ketone. Immediate precipitation occurred in most cases, and in others crystallisation commenced within 1 hr. at 0°. The mixtures were kept at 0° for several days, after which the crystals were filtered off, washed with ethanol containing a little of the carbonyl compound and finally with dry ether, and dried at 100° *in vacuo*. All the condensation products described below are slowly hydrolysed in water, and all gave within a few minutes the characteristic test

for the relevant aldehyde or ketone with cold 2 : 4-dinitrophenylhydrazine reagent in 2N-hydrochloric acid. The m. p.s tend to vary according to the mode of heating.

(a) *With acetaldehyde.* Colourless needles of *bis*-(*1-ethylidene-3 : 5 : 5-trimethylpyrazolinium*) *hexachlorostannate* were precipitated immediately, in good yield, m. p. 160—161° (decomp.) [Found : C, 31·6; H, 5·1; Cl, 35·0. $(C_8H_{15}N_2)_2SnCl_6$ requires C, 31·5; H, 4·9; Cl, 34·9%].

(b) *With propaldehyde.* The corresponding 1-*propylidene* derivative separated immediately as colourless plates, m. p. 220—221° (decomp.) [Found: C, 33·6; H, 5·4; Cl, 33·2. $(C_9H_{17}N_2)_2SnCl_6$ requires C, 33·8; H, 5·3; Cl, 33·4%].

(c) *With butaldehyde.* A plate-like mass of the 1-*butylidene* derivative separated immediately in very good yield, and had m. p. 190—195° (decomp.) [Found : C, 35·2; H, 5·7; Cl, 31·8; Sn, 17·9. $(C_{10}H_{19}N_2)_2SnCl_6$ requires C, 36·0; H, 5·7; Cl, 32·0; Sn, 17·8%].

(d) *With* isovaleraldehyde. An immediate white precipitate of the 1-3′-*methylbutylidene* derivative, m. p. 214° (decomp.), was formed in good yield [Found : C, 37·2; H, 6·0; Cl, 31·1. $(C_{11}H_{21}N_2)_2SnCl_6$ requires C, 38·1; H, 6·1; Cl, 30·8%]. (This specimen had been kept for several weeks before analysis for C and H, and had probably lost some aldehyde by hydrolysis in air.)

(e) *With crotonaldehyde.* Pale yellow crystals were formed in a few minutes, the ultimate yield of *bis*-(*1-but-2′-enylidene-3 : 5 : 5-trimethylpyrazolinium*) *hexachlorostannate*, m. p. 188° (decomp.), being good [Found : C, 35·9; H, 5·0; Cl, 32·1. $(C_{10}H_{17}N_2)_2SnCl_6$ requires C, 36·2; H, 5·1; Cl, 32·2%].

(f) *With tiglic aldehyde.* Clear yellow prisms of the 1-(2-*methylbut-2-enylidene*) derivative began to separate at room temperature within 1 hr. and the yield was good after 2 days at 0°; it had m. p. 176° (decomp. with earlier reddening) [Found : C, 38·2; H, 5·5; Cl, 30·8; Sn, 17·2. $(C_{11}H_{19}N_2)_2SnCl_6$ requires C, 38·3; H, 5·5; Cl, 30·9; Sn, 17·2%].

(g) *With benzaldehyde.* The 1-*benzylidene* derivative separated almost immediately as a colourless crystalline powder, m. p. 225° (decomp.) [Found : C, 41·8; H, 4·4; Cl, 28·9; Sn, 16·2. $(C_{13}H_{17}N_2)_2SnCl_6$ requires C, 42·5; H, 4·6; Cl, 29·0; Sn, 16·2%]. A portion of the product was shaken with a mixture of N-sodium hydroxide and ether, and the ether layer was washed with water. Small aliquot parts of the ether extract were then treated with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid and with phenylhydrazine respectively, yielding the corresponding hydrazones of benzaldehyde, m. p.s 237° and 158°. The bulk of the ether extract was then treated with dry hydrogen chloride; an oily solid was formed, which, after recrystallisation, was shown to be the hydrochloride of 3 : 5 : 5-trimethylpyrazoline, m. p. 176°.

(h) *With cinnamaldehyde.* Addition of this aldehyde gave a reddish-yellow solution which rapidly deposited bright yellow crystals of the 1-*cinnamylidene* derivative, m. p. 238° (decomp.) [Found : C, 45·6; H, 4·9; Cl, 27·0. $(C_{15}H_{19}N_2)_2SnCl_6$ requires C, 45·8; H, 4·8; Cl, 27·1%].

(i) *With acetone.* The *iso*propylidene derivative was described in Parts I and VIII (*locc. cit.*) as cubes. Prepared as here described, however, the crystals were unlike cubes but the composition and m. p. were identical. The difference in crystal habit may be due to the presence, in the liquors of the previous preparations, of hydrochloric acid, which would cause formation of some mesityl oxide. Mesityl oxide itself does not form a condensation product with the chlorostannate of 3 : 5 : 5-trimethylpyrazoline in alcoholic solution, but if it contains a little acetone it yields crystals which appear to be cubes visually but are not truly cubic when examined under the polarising microscope. They yield the 2 : 4-dinitrophenylhydrazone of acetone.

(j) *With other carbonyl compounds.* Similar products, which, however, were not analysed, were obtained with glyoxal (deep-red hygroscopic mass), *m*- and *p*-nitrobenzaldehyde and vanillin (yellow solids), acetylacetone (colourless), terephthalaldehyde (very insoluble, deep yellow solid), and furfuraldehyde (colourless solid which decomposed rapidly in a desiccator).

Reaction of Bis-(*5-methylpyrazolinium*) *Hexachlorostannate with Carbonyl Compounds.*—5-Methylpyrazoline (b. p. 91°/97 mm.; 4·4 c.c.), prepared from crotonaldehyde and hydrazine hydrate (von Rothenburg, *J. pr. Chem.*, 1895, **52**, 52), was added to a solution of stannic chloride pentahydrate (8·5 g.) in concentrated hydrochloric acid (5 c.c.), but it was not possible to crystallise a pure specimen of the chlorostannate of the above base. Evaporation *in vacuo* yielded a hygroscopic mass from a syrupy liquor. This was therefore dissolved in ethanol (30 c.c.), a small residue of hydrazine dihydrochloride being filtered off, and aliquot parts of the ethanolic solution were then added to approx. equal volumes of aldehyde or ketone. The precipitates were washed and dried as described in the previous section. They were all tested for the presence of hydrazine salts (iodate titration) and found to be free from contamination. All gave characteristic tests with 2 : 4-dinitrophenylhydrazine.

(a) *With acetone.* Immediate crystallisation of *bis*-(*5-methyl-1-isopropylidenepyrazolinium*)

hexachlorostannate occurred, m. p. 196° [Found : C, 28·5; H, 4·5; Cl, 36·6; Sn, 20·4. $(C_7H_{13}N_2)_2SnCl_6$ requires C, 28·9; H, 4·6; Cl, 36·6; Sn, 20·4%].

(b) *With ethyl methyl ketone.* An oil separated immediately, which solidified to a white powder when shaken with ethanol; this 1-sec.-*butylidene* derivative had m. p. 155—157° [Found : C, 31·7; H, 4·8; Cl, 35·0. $(C_8H_{15}N_2)_2SnCl_6$ requires C, 31·5; H, 4·9; Cl, 34·9%].

(c) *With crotonaldehyde.* Yellow prisms of the 1-*but*-2′-*enylidene* derivative separated rapidly, m. p. 128—130° (decomp.) [Found : C, 32·1; H, 4·2; Cl, 35·1; Sn, 19·5. $(C_8H_{13}N_2)_2SnCl_6$ requires C, 31·7; H, 4·3; Cl, 35·1; Sn, 19·6%].

(d) *With benzaldehyde.* The 1-*benzylidene* derivative was precipitated immediately, m. p. 203° (decomp.) [Found : C, 38·3; H, 3·9; Cl, 31·2; Sn, 17·6. $(C_{11}H_{13}N_2)_2SnCl_6$ requires C, 38·9; H, 3·8; Cl, 31·4; Sn, 17·6%].

(e) *With cinnamaldehyde.* The 1-*cinnamylidene* derivative, formed immediately, was deep yellow, m. p. 210° (decomp.) [Found : C, 43·4; H, 4·2; Cl, 29·0. $(C_{13}H_{15}N_2)_2SnCl_6$ requires C, 42·8; H, 4·1; Cl, 29·2%].

No satisfactory solid products could be isolated when acetaldehyde and butaldehyde were used; terephthalaldehyde, on the other hand, gave an immediate deep-yellow precipitate.

Reaction of Bis-(4 : 5-*dimethylpyrazolinium*) *Hexachlorostannate with Carbonyl Compounds.*—A mixture of hydrazine (95%; 1 g.) and tiglic aldehyde (2·2 g.) in dry methanol (10 c.c.) was heated under reflux for 2 hr., and to the cooled product was added a solution of stannic chloride pentahydrate (4·4 g.) in dilute hydrochloric acid. Evaporation of the resulting solution, first on the steam-bath and then *in vacuo*, furnished a pale yellow syrup; this was diluted with ethanol, and the solution, after having been filtered from some hydrazine dihydrochloride, was added in portions to the aldehydes and ketones noted below. Immediate precipitation of crystalline solids occurred. The products were washed and dried as previously described, and shown to be free from hydrazine salts; all were shown to contain aldehyde or ketone residues.

(a) *With acetone. Bis-*(4 : 5-*dimethyl*-1-iso*propylidenepyrazolinium*) *hexachlorostannate* separated as colourless crystals, m. p. 210—211° [Found : C, 32·3; H, 4·9; Cl, 34·8; Sn, 19·5. $(C_8H_{15}N_2)_2SnCl_6$ requires C, 31·5; H, 4·9; Cl, 34·9; Sn, 19·5%].

(b) *With ethyl methyl ketone.* The 1-sec.-*butylidene* derivative separated as a crystalline solid, m. p. 198—199° [Found : C, 33·8; H, 5·3; Cl, 33·7; Sn, 18·8. $(C_9H_{17}N_2)_2SnCl_6$ requires C, 33·8; H, 5·3; Cl, 33·4; Sn, 18·7%] : this ketone could not be condensed with the chlorostannate of 3 : 5 : 5-trimethylpyrazoline, possibly because of steric influences.

(c) *With benzaldehyde.* The 1-*benzylidene* derivative separated at first as an oil which, when scratched and cooled, gave a very pale buff-coloured solid, m. p. 185° (decomp.) [Found : C, 40·4; H, 4·4; Cl, 30·2. $(C_{12}H_{15}N_2)_2SnCl_6$ requires C, 40·8; H, 4·3; Cl, 30·2%].

(d) *With cinnamaldehyde.* The deep-yellow 1-*cinnamylidene* derivative had m. p. 193° (decomp.) [Found : C, 44·4; H, 4·5; Cl, 28·0; Sn, 15·8. $(C_{14}H_{17}N_2)_2SnCl_6$ requires C, 44·4; H, 4·5; Cl, 28·1; Sn, 15·7%].

Bis-(1 : 3 : 5 : 5-*tetramethylpyrazolinium*) *Hexachlorostannate.*—1 : 3 : 5 : 5-Tetramethylpyrazolinium iodide, prepared according to Curtius and Wirsing (*loc. cit.*), was dissolved in sodium hydroxide solution, and the free base was extracted with ether. The ether extract, washed with water and acidified with concentrated hydrochloric acid, was evaporated, finally to dryness, *in vacuo* over sulphuric acid and sodium hydroxide. The resulting hygroscopic, crystalline chloride, on treatment with the calculated quantity of stannic chloride in acetone solution, yielded the crude *hexachlorostannate*; it was recrystallised from acetone by addition of dry ether, forming colourless needles, m. p. 196° [Found : C, 28·2; H, 5·1; Cl, 36·5; Sn, 20·2. $(C_7H_{15}N_2)_2SnCl_6$ requires C, 28·7; H, 5·1; Cl, 36·4; Sn, 20·3%]. It gave no precipitate, even after long standing, when mixed in concentrated alcoholic solution with cinnamaldehyde, and the chlorostannate was recovered unchanged on adding ether.

Bis-(1 : 5-*dimethylpyrazolinium*) *Hexachlorostannate.*—This *salt* was obtained as colourless crystals, m. p. 207° (decomp.), when 1 : 5-dimethylpyrazoline, prepared according to von Auwers and Broche (*Ber.*, 1922, **55**, 3880), was added to a dry ethanol solution of stannic chloride containing excess of hydrogen chloride [Found, in material dried *in vacuo* at 56° : C, 22·3; H, 4·2; Cl, 40·2; Sn, 22·3. $(C_5H_{11}N_2)_2SnCl_6$ requires C, 22·6; H, 4·2; Cl, 40·2; Sn, 22·4%]. It was freely soluble in acetone from which it was recovered unchanged on addition of ether. Its solutions in ethanol yielded no precipitate with cinnamaldehyde, even on long standing at 0°.

Bis-[1 : 1(?) : 5-*trimethylpyrazolinium*] *Hexachlorostannate.*—A vigorous reaction occurred on mixing of 5-methylpyrazoline (9 c.c.) with methyl iodide (6 c.c.), the product being soluble in ethanol, from which 1 : 5-*dimethylpyrazoline methiodide* crystallised as colourless plates, m. p. 171—172° (Found : C, 29·5; H, 5·4; I, 53·0. $C_6H_{13}N_2I$ requires C, 30·0; H, 5·4; I, 53·0%).

This compound (0·65 g.) was heated under reflux for 8 hr. with ethanol and freshly-precipitated silver chloride (1 g.), the mixture being then stored for 2 days. After filtration to remove silver salts, the solution was evaporated *in vacuo*, yielding colourless needles (0·25 g.) which, on treatment with excess of stannic chloride in ethanol, gave the corresponding *hexachlorostannate*, m. p. 228—230° [Found: C, 26·1; H, 4·6; Cl, 38·1; Sn, 21·4. $(C_6H_{13}N_2)_2SnCl_6$ requires C, 25·8; H, 4·7; Cl, 38·2; Sn, 21·3%]; this is only sparingly soluble in ethanol, and was unchanged on treatment with acetone or cinnamaldehyde.

These two compounds presumably contain the 1 : 1 : 5-trimethylpyrazolinium ion. The secondary amino-group in pyrazolines is more basic than $N_{(2)}$ (Curtius and Wirsing, *loc. cit.*; von Auwers and Heimke, *Annalen*, 1927, **458**, 186) and substitution of a methyl group for a hydrogen atom at $N_{(1)}$ should further increase the basic character. 1 : 5-Dimethylpyrazoline would accordingly be methylated at $N_{(1)}$, not at $N_{(2)}$. This view is supported by the work of Theilacker and Leichtle (*Annalen*, 1951, **572**, 121).

1-*Cinnamylidene*-3 : 5 : 5-*trimethylpyrazolinium Chloride*.—3 : 5 : 5-Trimethylpyrazolinium chloride (1 g.), dissolved in dry ethanol (2 c.c.), was treated with cinnamaldehyde (2 c.c.), and the solution was boiled for a few minutes, and set aside for 1 hr.; addition of dry ether (10 c.c.) then gave yellow needles of the *chloride* of the 1-cinnamylidene derivative, m. p. 162° (decomp.). It was necessary to wash it with dry ether containing cinnamaldehyde, and finally with dry ether [Found, in material dried *in vacuo* at 100°: C, 66·8; H, 7·2; Cl, 13·4. $C_{15}H_{19}N_2Cl$ requires C, 68·8; H, 7·3; Cl, 13·5%]. (The low C value may be due to slight loss of aldehyde during the weighing.) The salt gave the characteristic phenylhydrazone of cinnamaldehyde, m. p. 168°, and on treatment with stannic chloride in ethanol yielded an immediate precipitate of yellow bis-(1-cinnamylidene-3 : 5 : 5-trimethylpyrazolinium) hexachlorostannate, m. p. 238°, identical with the product described on p. 2431.

Bis-(N-*methyldimethylketazinium*) *Hexachlorostannate*.—[This salt was isolated in an attempt to prepare 1 : 3 : 5 : 5-tetramethylpyrazolinium chlorostannate and, further, to determine whether this would condense with acetone to give an *iso*propylidene derivative (cf. 3 : 5 : 5-trimethyl*iso*propylidenepyrazolinium chlorostannate from hydrazine hydrochloride, Part VIII, *loc. cit.*). With methylhydrazine hydrochloride, however, there was no ring closure, or isomerisation, to a pyrazoline.] Methylhydrazine hydrochloride (2 g.; prepared as hygroscopic needles from the sulphate by addition of the calculated quantity of aqueous barium chloride solution, and evaporation of the filtrate to which a little hydrochloric acid had been added) and anhydrous stannic chloride (2·6 g.) were mixed in dry acetone. A white precipitate appeared in a few minutes, whereupon the mixture was boiled under reflux. After 2 hr. there appeared, on cooling, a mixture of large clear rhombs and a microcrystalline powder, but further heating caused all the solid to crystallise as rhombs. After 20 hr. the mixture was cooled in ice, and the solid *salt* was filtered off and washed with dry acetone; the yield was 5·0 g., and the m. p. 200—203° (decomp.) [Found, in material dried at 100° *in vacuo*: C, 27·5; H, 4·9; Cl, 36·8; Sn, 20·4; CH_6N_2, 15·9; C_3H_6O, 39·1. $(C_7H_{15}N_2)_2SnCl_6$ requires C, 28·7; H, 5·1; Cl, 36·4; Sn, 20·3; CH_6N_2, 15·7; C_3H_6O, 39·6%]. The methylhydrazine determination was by Andrews's method, the acetone by Messinger's. The low carbon value is typical of those found for ketazinium salts owing to surface decomposition by hydrolysis. Treatment with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid gave an instantaneous dense yellow precipitate.

Reactions of Phenylhydrazinium Salts with Acetone.—(a) *Bis*(*acetone-phenylhydrazonium*) *hexachlorostannate*. Though mixtures of stannic chloride and phenylhydrazine hydrochloride are very soluble in water, all attempts to crystallise phenylhydrazinium chlorostannate failed because phenylhydrazine hydrochloride, being less soluble, crystallised continuously on evaporation and cooling. However, *bis*(*acetone-phenylhydrazonium*) *hexachlorostannate* was readily obtained from concentrated aqueous solutions of the mixed salts (mol. ratio, 1 : 2) and acetone (3—4 vols.) at 0°, and further crops of similar crystals were obtained by adding small amounts of concentrated hydrochloric acid to the mother-liquor. Recrystallisation from warm acetone containing hydrochloric acid (5 : 1) yielded colourless needles and prisms, m. p. 155° (decomp.) [Found: C, 33·7; H, 4·0; $C_6H_8N_2$, 34·4; Cl, 33·8; Sn, 18·8. $(C_9H_{13}N_2)_2SnCl_6$ requires C, 34·3; H, 4·1; $C_6H_8N_2$, 34·3; Cl, 33·8; Sn, 18·9%].

(b) *Bis*(*acetone-phenylhydrazonium*) *hexabromostannate*. Clear reddish solutions of stannic bromide and phenylhydrazine hydrobromide (mol. ratio, 1 : 2) in acetone–hydrobromic acid yielded yellowish needles of the above-named *salt*, m. p. 158° (vigorous decomp.) [Found: C, 23·1; H, 2·7; $C_6H_8N_2$, 24·6; Br, 53·6; Sn, 13·1. $(C_9H_{13}N_2)_2SnBr_6$ requires C, 24·1; H, 2·9; $C_6H_8N_2$, 24·5; Br, 53·5; Sn, 13·3%]. A solution of this salt in dilute hydrobromic acid, on exposure to air for a few days, deposited yellowish plates of *bisphenylhydrazinium hexabromostannate*

[Found : $C_6H_8N_2$, 26·3; Br, 59·1; Sn, 14·5. $(C_6H_9N_2)_2SnBr_6$ requires $C_6H_8N_2$, 26·5; Br, 58·8; Sn, 14·6%].

(c) *Bis(acetone-phenylhydrazonium) hexachloroplatinate.* Phenylhydrazine hydrochloride (1·5 g.) was dissolved in a warm mixture of acetone (3 c.c.) and water (1 c.c.), and chloroplatinic acid (1·5 g.) was added to the cooled solution. The mixture effervesced slightly (nitrogen), rapidly if warmed, and deposited orange crystals of the above-named *hexachloroplatinate*, m. p. 152° (vigorous decomp. with earlier darkening) [Found : Cl, 30·1; Pt, 27·8. $(C_9H_{13}N_2)_2PtCl_6$ requires Cl, 30·1; Pt, 27·6%].

(d) *Bis-(3 : 5 : 5-trimethyl-1-phenylpyrazolinium) hexachlorostannate.* A solution containing stannic chloride pentahydrate (15 g.), phenylhydrazine hydrochloride (12 g.), concentrated hydrochloric acid (2 c.c.), and acetone (40 c.c.) was boiled under reflux for 20 hr., the dark liquid depositing yellowish crystals (5 g.). Another crop (6 g.) was obtained from the mother-liquor by continuing the refluxing, with addition of a little more hydrochloric acid, for a further 20 hr. The crude products contained traces of acetone-phenylhydrazonium chlorostannate, described above (iodate titration), and were accordingly recrystallised from acetone–dilute hydrochloric acid (4 : 1), yielding colourless cubes of *bis-(3 : 5 : 5-trimethyl-1-phenylpyrazolinium) hexachlorostannate*, m. p. 230—231° (decomp.) [Found : C, 39·1; H, 4·7; Cl, 29·9; Sn, 16·7. $(C_{12}H_{17}N_2)_2SnCl_6$ requires C, 40·6; H, 4·8; Cl, 30·0; Sn, 16·8%]. Although this was produced in acetone solution no trace of acetone could be detected on testing with the usual reagent and, moreover, attempts to prepare condensation products, by treating its cold alcoholic solutions with aldehydes, failed. A sample of the salt in aqueous acetone, on treatment with chloroplatinic acid, gave orange crystals of bis-(3 : 5 : 5-trimethyl-1-phenylpyrazolinium) hexachloroplatinate, m. p. 180° (decomp.) [Found : Cl, 27·3; Pt, 24·8. Calc. for $(C_{12}H_{17}N_2)_2PtCl_6$: Cl, 27·1; Pt, 24·8%].

Condensation of Acetone and Bis-(3-isobutenyl-5 : 5-dimethylpyrazolinium) Hexachlorostannate.—Hydrazine (95%; 0·45 c.c.) was added slowly to well-cooled phorone (1·83 g.). A violent reaction occurred, and after some hours at 20° the mixture was warmed to 60° and treated with dry acetone (20 c.c.), anhydrous stannic chloride (0·8 c.c.), and hydrogen chloride (0·5 g.) in methanol (1·2 c.c.). Crystals separated after the mixture had stood for a week at 0°; they were washed with dry acetone followed by dry ether and were dried *in vacuo* at 100° (loss in wt. at 100°, 1·5%); m. p. 189—191° (decomp.) [Found : C, 38·6; H, 6·4; Cl, 29·2; C_3H_6O, 25·4. $(C_{12}H_{21}N_2)_2SnCl_6,H_2O$ requires C, 39·1; H, 6·0; Cl, 28·9; C_3H_6O, 31·6%]. Except for the acetone value, the experimental figures agree reasonably with those required for *bis-(3-isobutenyl-5 : 5-dimethyl-1-isopropylidenepyrazolinium) hexachlorostannate*; the low acetone value may be due to incomplete liberation of acetone from the 3-*iso*butenyl group which has been shown to be resistant to hydrolysis (von Auwers and Kreuder, *Ber.*, 1925, **58**, 1982; cf. Kishner, *Chem. Zentr.*, 1913, ii, 2130). These values nevertheless indicate that acetone does condense with the chlorostannate of 3-*iso*butenyl-5 : 5-dimethylpyrazoline (which requires acetone, 18%, assuming complete hydrolysis of the *iso*butenyl group).

Acknowledgment is made to the University Council for a grant from the Staff Research Fund for some of the materials used; also to R. von Holdt, B.Sc., for the combustion analyses.

UNIVERSITY OF CAPE TOWN. [*Received, March 3rd*, 1954.]

The Cyclisation of Some Substituted Phenylsuccinic Acids.

By V. Askam and W. H. Linnell.

[Reprint Order No. 5221.]

The cyclisation of derivatives of phenylsuccinic acid has been investigated as a route to the corresponding indane-1-carboxylic acids required in the synthesis of analogues of cortical hormones (see also Linnell, Mathieson, and Modi, *J.*, 1953, 3257).

Cyclisation by the Friedel–Crafts and the hydrogen fluoride method has been investigated and evidence is given of the sensitivity of anhydrous hydrogen fluoride to activating and deactivating influences in the cyclisation process.

Phenylsuccinic acid has been cyclised by sulphuric acid (Speight, Stevenson, and Thorpe, *J.*, 1924, 2185), by fluorosulphonic acid (Baker, Coates, and Glockling, *J.*, 1951, 1376), and by the Friedel–Crafts method (Baker and Leeds, *J.*, 1948, 974). *p*-Methoxyphenylsuccinic acid was reported resistant to cyclisation by sulphuric acid and by phosphoric oxide (Chatterjee and Barpujari, *J. Indian Chem. Soc.*, 1940, **17**, 292).

The derivatives of phenylsuccinic acid used in the present work were prepared by modifications of the original method of Baker and Lapworth (*J.*, 1925, 560). Nitrobenzene was used as solvent in cyclisations by the Friedel–Crafts method : intermediate acid chlorides or anhydrides were not isolated.

m-Methoxyphenylsuccinic acid when cyclised by the Friedel–Crafts method at 80° gave 6-methoxy-3-oxoindane-1-carboxylic acid, the constitution of which was verified by oxidation with alkaline potassium permanganate to 4-methoxyphthalic acid. In addition, a small amount of an isomer was produced, presumably 4-methoxy-3-oxoindane-1-carboxylic acid formed by cyclisation into the position *ortho* to the methoxy-group.

Under similar conditions, 3 : 4-dimethoxyphenylsuccinic acid gave 5 : 6-dimethoxy-3-oxoindane-1-carboxylic acid. The consitution of this compound was established by decarboxylation to the known 5 : 6-dimethoxyindanone.

Both of these phenylsuccinic acids were readily cyclised by anhydrous hydrogen fluoride, and quantitative determination of the products (see Table) showed that cyclisation had occurred almost to the theoretical extent.

In contrast, *p*-methoxyphenylsuccinic acid could not be cyclised under the Friedel–Crafts conditions adequate for the above acids. The product was mainly a tar from which no ketone could be isolated. When a temperature of 150° was used, only small amounts (less than 5%) of ketonic material were isolated in addition to tar. By a comparable procedure, β-*p*-methoxyphenylglutaric acid has been cyclised with simultaneous demethylation (Hey and Kohn, *J.*, 1949, 3177). Molten sodium chloride–aluminium chloride (Bruce, Sorrie, and Thompson, *J.*, 1953, 2403) also gave less than 5% of ketonic material. It appears that *p*-methoxyphenylsuccinic acid, having a carboxyl group nearer the aromatic ring, is far more resistant to cyclisation than β-*p*-methoxyphenylglutaric acid (see Badger, Campbell, and Cook, *J.*, 1949, 1084). *p*-Methoxy- and *p*-hydroxy-phenylsuccinic acid gave no detectable ketonic product by the action of anhydrous hydrogen fluoride (28 hours), and starting material was recovered.

p-Ethylphenylsuccinic anhydride was cyclised by the Friedel–Crafts method to 5-ethyl-3-oxoindane-1-carboxylic acid (isolated *via* the semicarbazone); yields from the acid chloride were inferior. Reaction of *p*-ethylphenylsuccinic acid with anhydrous hydrogen fluoride is slow, and a prolonged period of reaction (14 days) was necessary for the reaction to approach completion.

The results of the action of anhydrous hydrogen fluoride on derivatives of phenylsuccinic acid show this reagent to be peculiarly sensitive to activating and deactivating influences. A number of derivatives were cyclised by anhydrous hydrogen fluoride and the amounts of keto-acid in the crude products of the reaction determined as the 2 : 4-dinitrophenylhydrazones. In addition, since the products were clean and free from tar, in most cases it was possible to make an approximate determination by direct titration of the product, on the assumption that it consisted of a mixture of dibasic and monobasic (keto-)acid only. The

results, which are roughly parallel, are given in the Table below. Phenylsuccinic acid is largely unchanged by the action of anhydrous hydrogen fluoride (28 hours), which illustrates the deactivating effect of a carboxyl group α to a phenyl nucleus (Badger, Campbell, and Cook, *loc. cit.*; Ansell and Hey, *J.*, 1950, 2874). This effect is offset, to some extent, by *p*-alkyl groups. A *m*-methoxy-group, which specifically activates the position into which cyclisation occurs, entirely overcomes the deactivating effect. It appears that anhydrous hydrogen fluoride, being highly selective in operation, offers a more reliable means for comparing the relative ease of cyclisation of carboxylic acids than does anhydrous aluminium chloride.

Acid	Time of reaction	Keto-acid (%) as dinitrophenylhydrazone	Keto-acid (%) by titration
Phenylsuccinic	28 hr.	4	6
Phenylsuccinic	48 ,,	6	11
Phenylsuccinic (anhydride)	28 ,,	11	15
p-Methoxyphenylsuccinic	28 ,,	0	—
p-Hydroxyphenylsuccinic	28 ,,	0	—
p-Ethylphenylsuccinic	28 ,,	21	25
p-Ethylphenylsuccinic	14 days	83	89
m-Methoxyphenylsuccinic	28 hr.	100	102
3 : 4-Dimethoxyphenylsuccinic	28 ,,	96	100

Experimental

Preparation of Acids.—m-*Methoxyphenylsuccinic acid.* (*a*) *m*-Hydroxybenzaldehyde (110 g.) was dissolved in a solution from sodium (21 g.) in alcohol (700 ml.). Methyl iodide (141 g.) was added to the cool solution and the mixture set aside for 3 days. Alcohol (approx. 500 ml.) was then removed by distillation, the residue was poured into water, and the mixture extracted with ether. The extract was dried (Na_2SO_4) and fractionally distilled, to give *m*-methoxybenzaldehyde (86 g., 70%), b. p. 103—105°/8 mm., n_D^{25} 1·5508. (*b*) Piperidine (1 ml.) was added to a mixture of *m*-methoxybenzaldehyde (34 g.) and ethyl cyanoacetate (29 g.); heat was evolved and water separated. The mixture was set aside for 2 hr., with occasional shaking, after which alcohol (40 ml.) was added followed by sodium cyanide (16 g.) in water (20 ml.). A solid was deposited overnight and was removed and freed, as far as possible, from dark liquid by pressure; it was then hydrolysed by 4 hours' refluxing with concentrated hydrochloric acid (450 ml.). The cooled solution was filtered and the crude product crystallised, with constant stirring, from water (300 ml.). The yield was 28 g. (45% from *m*-methoxybenzaldehyde) and the m. p. 174—175° (Found: C, 59·0; H, 5·4; MeO, 13·8%; equiv., 112·6. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4; MeO, 13·85%; equiv., 113·1).

p-*Methoxyphenylsuccinic acid.* By method (*b*), *p*-anisaldehyde (41 g.) gave a crude product (47·5 g.) which, when crystallised from water (1500 ml.), gave *p*-methoxyphenylsuccinic acid (39·4 g., 59%), m. p. 203—203·5°.

p-*Ethylphenylsuccinic acid.* *p*-Ethylbenzaldehyde (29 g.), ethyl cyanoacetate (24·5 g.), piperidine (1 ml.), and benzene (50 ml.) were refluxed together in a Dean–Stark apparatus. When the theoretical amount of water had been evolved, ether was added, and the mixture shaken with 5% hydrochloric acid, and then with water until the washings were neutral to litmus. The ethereal solution was dried (Na_2SO_4) and fractionally distilled. The separation of a sharp fraction was difficult owing to decomposition or chemical change which occurred on distillation. The fraction distilling at 130—140°/0·05 mm. (22·9 g.) was mixed with alcohol (15 ml.), and sodium cyanide (6·2 g.) in water (11 ml.) was added. The mixture was set aside overnight, then diluted with water (400 ml.) and acidified with concentrated hydrochloric acid (30 ml.). A heavy yellow oil was precipitated from which the supernatant liquid was decanted. The oil was heated under reflux for 6 hr. with concentrated hydrochloric acid (350 ml.), and the crude product removed by filtration from the cooled mixture. Crystallisation from water (1200 ml.) gave pale yellow p-*ethylphenylsuccinic acid* (12·75 g., 27% from *p*-ethylbenzaldehyde), m. p. 188—189°. Recrystallisation from alcohol (30 ml.) gave a colourless product (8·5 g.) of the same m. p. (Found: C, 64·9; H, 6·3. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). The *dimethyl ester* is a colourless liquid, b. p. 155°/8 mm. (Found: C, 67·1; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·25%).

Other derivatives of phenylsuccinic acid were prepared by methods previously described in the literature, *viz.*, phenylsuccinic acid (*Org. Synth.*, Coll. Vol. I, 1st Edn., p. 440): *p*-hydroxyphenylsuccinic acid [Chrzaszezewska, *Roczn. Chem.*, 1925, **5**(1—3), 33]: 3 : 4-dimethoxyphenyl-

succinic acid (Richardson, Robinson, and Seijo, *J.*, 1937, 835): phenylsuccinic anhydride (Robinson and Young, *J.*, 1935, 1414).

Cyclisation Experiments.—Reactions involving anhydrous hydrogen fluoride were conducted in " Polythene " screw-cap bottles. For the quantitative determinations (see Table), the solution of the acid (3 g.) in anhydrous hydrogen fluoride (approx. 30 ml.) was set aside for the required time, after which it was poured into a " Polythene " beaker and allowed to evaporate in a good draught in the fume cupboard. The residue was air-dried at 40°. Titrations of the residue were performed in aqueous alcohol. Quantitative determinations by 2 : 4-dinitrophenylhydrazine were conducted by Sharp's method (*Analyst*, 1951, **76**, 215, method *h*). Hot water (40 ml.) was used for the final washing of each precipitate.

m-*Methoxyphenylsuccinic Acid.*—(*a*) The acid (10 g.) and pure thionyl chloride (15 ml.) were refluxed together and, when the reaction was complete, the excess of chloride was removed at the water-pump. The residue was added (with the aid of 15 ml. of nitrobenzene) to a solution of anhydrous aluminium chloride (6·25 g.) in nitrobenzene (75 ml.). The mixture was heated for 30 min. in an oil-bath at 80—85° and then poured on crushed ice and dilute hydrochloric acid. Nitrobenzene was removed in steam, conditions being adjusted so that the volume of solution remaining was approx. 350 ml. The crude product (5·4 g.) deposited from this solution on cooling was recrystallised from alcohol (30 ml.) to give 6-*methoxy*-3-*oxoindane*-1-*carboxylic acid* as colourless needles (4·3 g., 47%), m. p. 186·5—187·5°, unchanged on further crystallisation (Found: C, 64·0; H, 4·7; MeO, 15·1%; equiv., 208·2. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9; MeO, 15·05%; equiv., 206·2). The *semicarbazone* crystallised from aqueous alcohol in colourless felted needles, m. p. 227° (decomp.) (Found: C, 54·7; H, 5·0; N, 15·7. $C_{12}H_{13}O_4N_3$ requires C, 54·75; H, 4·95; N, 16·0%). The combined aqueous mother-liquors from three experiments as above were evaporated to low volume; a dark brown solid (4·7 g.) separated from the cooled solution. Two crystallisations from alcohol gave colourless needles (1 g.), m. p. 216° (decomp.), presumably 4-*methoxy*-3-*oxoindane*-1-*carboxylic acid* (Found C, 64·3; H, 4·7; MeO, 15·0%; equiv., 208·2).

(*b*) *m*-Methoxyphenylsuccinic acid (20 g.) was dissolved in anhydrous hydrogen fluoride (approx. 100 ml.). After 7 days, the solution was allowed to evaporate to dryness and the residue crystallised from water (1000 ml.) to give 6-methoxy-3-oxoindane-1-carboxylic acid (9 g., 49%). By evaporation of the mother-liquors and crystallisation of the product as above, the isomeric keto-acid (1·5 g.) was obtained in addition to mixtures of the two isomers. The products of the reaction are apparently volatile in steam as only two-thirds of the total solids was recovered when the solution was evaporated to low volume. 6-Methoxy-3-oxoindane-1-carboxylic acid (1 g.) was oxidised by alkaline potassium permangantae (Hey and Kohn, *J.*, 1949, 3177). The crude product (0·85 g.) when crystallised from water gave 4-methoxyphthalic acid, m. p. and mixed m. p. 163·5° (authentic sample, 164°). The anhydride prepared by vacuum sublimation had m. p. 89·5—90·5° with shrinking at 87°.

3 : 4-*Dimethoxyphenylsuccinic Acid.*—(*a*) The acid (38·2 g.) was refluxed with pure thionyl chloride (60 ml.), and the reaction completed as described above, with anhydrous aluminium chloride (21 g.) and nitrobenzene (280 ml.), the reaction time being 40 min. After the nitrobenzene had been removed, a dark brown solid (17 g.) was deposited from the cooled residual solution (830 ml.), and a further crop (8·7 g.) was collected after evaporation of the solution to 290 ml. Further evaporation gave tars. The two crops were combined and crystallised from methanol (150 ml.) and from water, to give 5 : 6-*dimethoxy*-3-*oxoindane*-1-*carboxylic acid* as colourless needles (13·5 g., 38%), m. p. 190—190·5° with softening at 184° (Found: C, 60·9; H, 4·95; MeO, 26·4%; equiv., 238·0. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1; MeO, 26·3%; equiv., 236·2). The *oxime* crystallised from aqueous alcohol as colourless needles, m. p. indefinite (darkens above 200°, almost black at 217°) (Found: C, 57·5; H, 5·4; N, 5·7. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2; N, 5·6%).

(*b*) The acid (5 g.) was dissolved in anhydrous hydrogen fluoride (50 ml.). After 28 hr., the solution was allowed to evaporate and the residue crystallised from water (170 ml.), to give pale buff needles (3·4 g., 73%), m. p. 185—186° (with softening at 183°) unchanged on further crystallisations from methanol and from ethanol. Since the crude product of this cyclisation contains almost 100% of keto-acid (see Table), the low m. p. must be ascribed to the presence of an isomer. 5 : 6-Dimethoxy-3-oxoindane-1-carboxylic acid (1 g.), quinoline (10 ml.), and copper bronze (1 g.) were heated together at 220—230°. After 10 min., the vigorous reaction had subsided. Ether was added to the cooled mixture and the copper bronze removed by filtration. Quinoline was removed by 15% hydrochloric acid. The acid solution was repeatedly extracted with ether, then all the ethereal solutions were combined, washed with sodium hydrogen

carbonate solution, and dried (Na_2SO_4). Evaporation of the ether gave pale yellow prisms (0·4 g.) which, when crystallised from toluene–light petroleum (b. p. 80—100°), gave 5 : 6-dimethoxyindanone as large yellow prisms, m. p. 114—116°. The 2-*m*-methoxybenzylidene derivative (Perkin, Ray, and Robinson, *J.*, 1926, 941) had m. p. 162·5—163°.

p-*Ethylphenylsuccinic Acid.*—(*a*) The acid (4·4 g.) was refluxed with acetyl chloride (25 ml.) : when the reaction was complete, the excess of acetyl chloride was removed at the water-pump. The general procedure used in the cyclisation of *m*-methoxyphenylsuccinic acid was then followed, with anhydrous aluminium chloride (5·6 g.) and nitrobenzene (50 ml.). After the nitrobenzene had been removed, an oil was separated from the aqueous solution by extraction with ether. Removal of the ether gave a viscous residue which was dissolved in alcohol (12 ml.). The alcoholic solution was heated, under reflux, for 15 min. with semicarbazide hydrochloride (3 g.) and sodium acetate (6 g.) in water (20 ml.). The mixture was cooled and filtered, and the residue washed with boiling alcohol (10 ml.) to remove unchanged *p*-ethylphenylsuccinic acid : the crude semicarbazone remained as a pale yellow powder (4·1 g., 79%), which crystallised from ethoxyethanol as colourless needles, m. p. 242° (decomp.). The crude semicarbazone (0·7 g.) was decomposed by refluxing it for 20 min. with concentrated hydrochloric acid (25 ml.). Water (10 ml.) was added, and the hot solution filtered. The filtrate was extracted with ether, and the washed and dried ethereal solution evaporated to a viscous residue (0·35 g.). Crystallisation from water (approx. 70 ml.) with seeding gave *5-ethyl-3-oxoindane-1-carboxylic acid* as colourless needles, m. p. 87—88° (Found : C, 70·7; H, 5·9. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone*, crystallised from alcohol–xylene, melts partly at 211° (Found : C, 56·6; H, 4·4; N, 14·2. $C_{18}H_{16}O_6N_4$ requires C, 56·2; H, 4·2; N, 14·6%).

(*b*) *p*-Ethylphenylsuccinic acid (4·4 g.) was dissolved in anhydrous hydrogen fluoride (approx. 40 ml.). After 14 days, the hydrogen fluoride was allowed to evaporate, and the residue was converted into the semicarbazone as above. The yield was 3·7 g., corresponding to 71% of 5-ethyl-3-oxoindane-1-carboxylic acid.

School of Pharmacy, University of London,
17 Bloomsbury Square, London, W.C.1.

[*Received, March 20th*, 1954.]

Studies in the Chemistry of Quadrivalent Germanium: Ion-exchange Studies of Solutions of Germanates.

By D. A. Everest and J. E. Salmon.

[Reprint Order No. 5066.]

Anion-exchange studies with a strongly basic exchanger show that, at pH values close to 9, germanium, in the form of the pentagermanate ion, is strongly adsorbed from germanate solutions, even in the presence of comparable concentrations of chloride. At both lower and higher pH values the adsorption of germanium falls off rapidly and in such a manner as to indicate a decrease in the concentration of pentagermanate ions in the solutions. From solutions with higher pH values, less polymerised (probably monogermanate) ions are adsorbed in place of the pentagermanate ions. In neutral and slightly acidic solutions, too, there is evidence, although less conclusive, of adsorption of a monomeric germanate ion.

The removal of adsorbed germanium from the resin on washing is interpreted as involving, as a first stage, the hydrolysis of the strongly adsorbed pentagermanate ion to the less strongly adsorbed monogermanate ion.

The chemical nature of germanium dioxide in solution over the pH range 4—13 has received considerable attention. The results of a series of pH titrations of germanium dioxide solutions of various concentrations with alkali have been interpreted as indicating the presence of the pentagermanate ion Ge_5O_{11}'' in solutions in the pH range 8·8—9·2. This is the region of the " isohydric point "—the point of intersection of the pH titration curves corresponding to the various concentrations of germanium dioxide. At higher pH values depolymerisation of the pentagermanate ion to the monogermanate ion, $HGeO_3'$,

was said to occur (Carpeni and Tchakarian, *Compt. rend.*, 1948, **226**, 725; Carpeni, *Bull. Soc. chim.*, 1948, 629). The isolation of crystalline potassium pentagermanate from a solution of germanium dioxide in 2M-potassium chloride at pH 9·2 (Tchakarian and Carpeni, *Compt. rend.*, 1948, **226**, 1094) lent support to the view that the pentagermanate ion was present in such solutions. Some of Carpeni's conclusions have been criticised by Souchay and others (Souchay and Teyssèdre, *Bull. Soc. chim.*, 1951, 938; Bye, *ibid.*, 1953, 390; Souchay, *ibid.*, p. 395). For instance, while Carpeni (*ibid.*, 1952, 1010; *loc. cit.*) believed that pentagermanic acid was the principal species present in pure germanium dioxide solutions, Souchay, who quoted and extended Roth and Schwartz's cryoscopic data (*Ber.*, 1926, **59**, 338), used these to support his view that monogermanic acid was present in such solutions and that this underwent first polymerisation to pentagermanate and then depolymerisation to monogermanate again with rise of pH.

Schwarz and Huf (*Z. anorg. Chem.*, 1931, **203**, 188) have interpreted the results of their dialysis experiments with solutions of germanium dioxide in aqueous potassium nitrate as showing the presence of a monomeric species below pH 5·5, of an increasing amount of pentagermanic acid between pH 5·5 and 8·4, and of monogermanate ion above pH 12·5. Between pH 8·8 and 12·5 these workers could get no useful results as a precipitate [considered by Tchakarian and Carpeni (*loc. cit.*) to be potassium pentagermanate] was formed on the membrane. Similar experiments by Brintzinger (*Z. anorg. Chem.*, 1948, **256**, 98) also indicated the presence of monogermanate ions in strongly alkaline media (pH >13).

The fact that germanium dioxide is soluble in water as well as in acid and alkaline solutions suggested that ion-exchange studies would provide a convenient method of determining the nature of the ions present in solution at various pH values—both in the presence and in the absence of other anions. Preliminary experiments showed that germanium was not adsorbed by the cation-exchanger Zeo-Karb 225 (in the hydrogen form) from solutions in the pH range 1—7, thus indicating the absence in them of germanium cations. Germanium was adsorbed, however, by the strongly basic anion-exchanger Amberlite I.R.A.-400 (in the hydroxide and the chloride form) from solutions with pH values in the range 4—13, even in the presence of comparable concentrations of chloride. Determinations of the quantities of the various species adsorbed and of the capacities of the resin samples used have permitted the determination of the ionic form in which the germanium is adsorbed at the various pH values.

Experimental

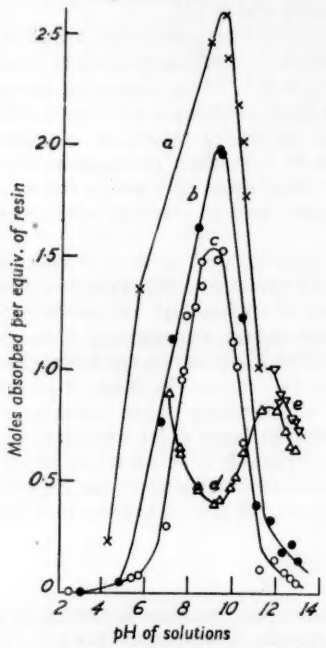
Solutions.—Stock solutions were prepared by dissolving pure germanium dioxide in boiled-out distilled water. These solutions contained 31—33 mmoles of germanium per l. [*i.e.*, in the range of stable concentrations (Gulzian and Muller, *J. Amer. Chem. Soc.*, 1932, **54**, 3142; Schwarz and Huf, *loc. cit.*)]. The pH of the solutions was raised by addition of sodium hydroxide and lowered by addition of hydrochloric acid. Chloride was added as sodium chloride. The solutions, containing a known amount of germanium (1·6—1·8 mmoles), were diluted to 75 ml. before addition of the resin.

Anion-exchanger.—Analytical-grade Amberlite I.R.A.-400 (supplied in the hydroxide form) was used throughout (0·25-g. samples) in either the hydroxide or the chloride form. The latter was obtained from the former by treatment with 2N-hydrochloric acid and was washed free from excess of acid and dried in the air before use.

Equilibrium Experiments.—At least 18 days, with frequent shaking, were allowed for equilibrium between solution and resin phases to be established (experiments extending over longer periods established that this was adequate). The solution was then filtered through a dry column (1 cm. internal diameter, 10 cm. long above the sealed-in sintered-glass disc of No. 2 grade porosity). The filtrate was retained, and aliquot portions of it were used for analysis and pH measurements. The resin was then transferred to the column and washed rapidly with water (*ca.* 50 ml.) under suction. In this way any solution adhering to the resin was quickly displaced and interaction between partly diluted solution and the resin was avoided. Very little of the adsorbed germanium was removed at this stage (see below) and these washings were rejected. After the column had been filled with water, a further 300—500 ml. of water were slowly passed through it to complete the washing. Since in this process

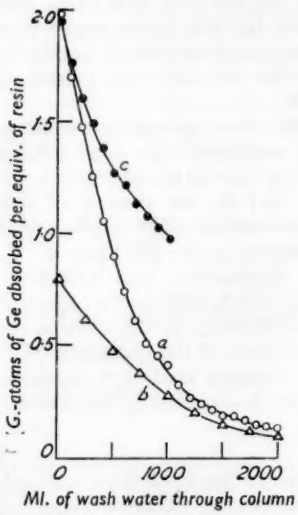
part of the germanium on the resin was displaced, the amount of this originally adsorbed was determined from the difference in germanium content in the original solution and in the filtrate. Any chloride adsorbed by the resin was then removed by elution with 500 ml. of 3N-nitric acid and determined in the eluate (the elution also removed the remainder of the germanium adsorbed). After being washed, the resin was converted completely into the chloride form by treatment with 500 ml. of 3N-hydrochloric acid and then washed until free from excess of acid. A final elution with 3N-nitric acid and a determination of the chloride thus removed gave the capacity of the resin sample. As this varied from sample to sample, the results have been expressed in terms of moles adsorbed per equiv. of resin.

FIG. 1. *Adsorption of germanium and chloride by I.R.A.-400.*



Mmoles added Ge	Mmoles added Cl	Resin form	Adsorbed on resin Ge	Adsorbed on resin Cl
1·6—1·8	0—0·3	OH	× *a*	—
1·6—1·8	0·8—1·0	Cl	● *b*	—
1·6—1·8	1·8	Cl	○ *c*	△ *d*
0	1·8	Cl	—	▽ *e*

FIG. 2. *Removal of germanium from I.R.A.-400 on washing.*



Elution with distilled water ..... ○ *a*; △ *b*
Elution with water from mixed-bed resin column ..... ● *c*

Analytical Methods.—Germanium was estimated iodometrically, after reduction to the bivalent state (Everest, *J.*, 1953, 4117). Chloride was determined gravimetrically as silver chloride. Measurements of pH were made with a commercial-type pH meter, a glass electrode and a saturated calomel electrode being used. For strongly alkaline solutions a Cambridge Instrument Company " Alki "-glass electrode was used.

RESULTS.—*Equilibrium experiments.* The quantities of germanium and chloride adsorbed by the resin in experiments with equimolecular quantities of germanium and chloride present (chloride added as the chloride form of the resin being included) are represented in Fig. 1 (curves *c* and *d*). The adsorption of germanium passes through a maximum at a pH of 9·0—9·2, a minimum in the adsorption of chloride occurring at the same point. The rapid decrease in adsorption of germanium on either side of this peak is accompanied by a marked increase in adsorption of chloride. Above pH 12 the adsorptions of both germanium and chloride decrease as a result of competitive adsorption of hydroxide. The starting point and extent of this competition are apparent from the results of blank experiments with chloride only present

which are also shown in Fig. 1. Above a pH value of 12 the amounts of chloride adsorbed fall below the value of 1 mole per equiv. of resin and the differences found indicate the moles of hydroxide ion adsorbed.

With half the amount of chloride or with no chloride present—except for traces, added as hydrochloric acid, to obtain solutions of low pH—the adsorption of germanium is higher at all pH values, particularly in the latter case. However, the shape of curves (*a* and *b* in Fig. 1) is substantially the same and the peak occurs at the same point.

Hydrolysis of the germanate form of Amberlite I.R.A.-400. As already mentioned (p. 2439), washing the resin resulted in the slow removal of the germanium adsorbed. The rate of removal depended to some extent on the rate of flow of the wash water, but when this was about 100 ml. per hr. 2 l. of water removed approximately 1 mmole of germanium from 0·25 g. of resin. The results of experiments in which every 100-ml. or 250-ml. fraction of the washings was collected and analysed for germanium content are shown in Fig. 2. It can be seen that the rate of desorption of germanium was markedly less if the distilled water used for washing was first passed through a column of Bio-Demineralit (mixed-bed) resin and care taken to exclude the carbon dioxide of the atmosphere.

When the resin was left in contact with a fixed amount of water, the amount of germanium adsorbed fell rapidly at first, then more slowly, and finally reached a constant value (Table 1).

TABLE 1. *Rate of desorption of germanium from Amberlite I.R.A.-400 (0·25 g. of chloride- and germanate-form) on contact with water (250 ml.) at room temperature.*

Time (hr.)	0	4	30	100	480	1150	1680
Ge on resin (mmoles)	1·35	1·21	1·09	0·99	0·90	0·84	0·84 *

* pH of aqueous phase = 7·56.

The number of germanium atoms present in one equivalent of the germanate ions adsorbed. If the results of the equilibrium experiments are expressed in terms of moles adsorbed per equiv. of resin, then the number of germanium atoms present in one equiv. of the germanate ions adsorbed (= R) may be found in the following ways:

(*a*) R = (moles of Ge adsorbed)/(1 − equivs. of other species adsorbed).

When hydroxide is one of the species adsorbed it has to be determined indirectly and this has to be done in two ways (Table 2).

TABLE 2. *The number of germanium atoms present in one equivalent of the germanate ions adsorbed* (R).

pH	R	Method *	pH	R	Method *	pH	R	Method *
(1) I.R.A.-400-(OH), 1·8 mmoles of Ge, 0—0·3 mmole of Cl.								
4·24	0·58	*a*	9·36	2·59	*a*	10·22	2·02	*a*
5·56	1·69	*a*	9·41	2·39	*a*	10·37	1·77	*a*
7·45	2·03	*a*	9·93	2·18	*a*	11·03	1·00	*a*
8·68	2·46	*a*						
(2) I.R.A.-400-(Cl), 1·66 mmoles of Ge, 0·7—0·9 mmole of Cl.								
7·71	2·31	*b*	7·71	2·30	*a*	9·10	2·59	*c*
9·20	2·66	*b*						
(3) I.R.A.-400-(Cl), 1·8 mmoles of Ge, 1·8 mmoles of Cl.								
6·92	2·69	*a*	9·12	2·44	*a*	11·28	0·57	*a*
7·52	2·68	*a*	9·34	2·53	*a*	11·96	0·81	*a*
7·74	2·66	*a*	9·86	2·11	*a*	12·34	0·68 † 0·56 ‡	*a*
8·38	2·73	*a*	10·08	2·09	*a*	12·66	0·49 † 0·38 ‡	*a*
8·38	2·57	*a*	10·42	1·77	*a*	12·84	0·39 † 0·30 ‡	*a*

* See text.

† Correction made for adsorption of hydroxide by assuming that the total adsorption of hydroxide is the same in the presence of germanium as it is in the blank experiment.

‡ Correction made for adsorption of hydroxide by assuming that the ratio of hydroxide to chloride adsorbed is the same in the presence of germanium as it is in the blank experiment.

(*b*) When the chloride form of the resin is used, but no other chloride is added:

R = (moles of Ge adsorbed)/(equivs. of Cl in solution at equilibrium)

since the germanium must take up the resin sites vacated by the chloride it displaces.

(*c*) When the resin is washed to the complete removal of germanium and an equivalent amount of the resin is converted into the hydroxide or carbonate form. This can be estimated by passing an excess of 0·5N-sodium chloride solution through the column and determining the alkali liberated in the effluent:

R = (moles of Ge adsorbed)/(equivs. of alkali)

The third method is tedious, as the complete removal of the germanium is difficult to achieve. However, both the second and the third method have the advantage that it is not necessary to know the capacity of the resin sample used. The results obtained by the three methods are shown in Table 2.

Discussion

The results of the experiments with equimolecular amounts of germanium and chloride [Table 2, (3)] indicate that below pH 9·4 the doubly charged pentagermanate ion (Ge_5O_{11}''; $R = 2·5$) is the only germanate ion adsorbed by the resin, at least down to pH 6·9. As the pH of the solutions is lowered the amount of pentagermanate adsorbed falls rapidly, its place being taken by chloride ion (Fig. 1). Although this could be caused by a repression of the ionisation of pentagermanic acid, the results of Roth and Schwartz, of Souchay, and of Schwarz and Huf (*locc. cit.*) provide strong evidence that depolymerisation of pentagermanic acid to a monomeric species offers a more likely explanation.

Souchay and Teyssèdre (*loc. cit.*) have pointed out that if Roth and Schwartz's cryoscopic data are interpreted in terms of the presence in germanium dioxide solutions of pentagermanic acid and its ions, then the pH of the solutions should be lower than the values actually found (*ca.* 6). Souchay (*loc. cit.*) attributes the slight acidity of the solutions to an equilibrium, $5H_2GeO_3 \rightleftharpoons Ge_5O_{11}'' + H_2O + 2H^+$, which is displaced well to the left. Any rise in pH will, however, increase the concentration of pentagermanate ions.

If, as Souchay implies, the monomeric species is a monogermanic acid, it must be a weak acid similar to, if not identical with, that present in solutions of high pH. The steady decrease in the values of R in the range of pH 8·68—4·24 with the minimum amount of chloride present [Table 2, (1)] indicates a progressive replacement of pentagermanate ions by less complex ions (*e.g.*, $HGeO_3'$, $R = 1$; cf. HGe_5O_{11}' for which $R = 5$) as the species adsorbed. However, we prefer not to base any quantitative conclusions on the results obtained with the hydroxide form of the resin in view of the fact that it certainly contained an unknown amount of carbonate which could not be taken into account when calculating the values of R. For example, the value found at pH 4·24, which would suggest the adsorption of a doubly ionised monogermanate ion ($R = 0·5$), seems unlikely, and a value of unity, as suggested above, might have been expected. Nevertheless, the values of R found at pH 7·71 at the intermediate chloride concentrations [Table 2, (2)], which are significantly below the value of 2·5, also provide support for the view that less complex ions are being adsorbed. Such ions cannot be so strongly adsorbed as the pentagermanate or chloride ions, however, as the last two are the only ones adsorbed at higher chloride-ion concentrations [Table 2, (3)].

The steady decrease in the values of R found at pH values above 9·4 (Table 2) shows that the adsorption of pentagermanate ions is giving way to the adsorption of less complex ions. They are apparently less readily adsorbed, for the initial stages of this replacement are accompanied by an increased adsorption of chloride (Fig. 1). The values are compatible with the view that replacement of Ge_5O_{11}'' by $HGeO_3'$ or by $[Ge(OH)_5(OH_2)]'$ occurs first ($R = 1$) and then, at about pH 11, replacement of these by GeO_3'' or $[Ge(OH)_6]''$ ions takes place ($R = 0·5$). The changes in the slopes of the curves of chloride and germanium adsorption (Fig. 1) at this pH also indicate the adsorption of a more strongly adsorbed ion.

If intermediate polymeric ions such as Ge_4O_9'' ($R = 2$), HGe_2O_5' ($R = 2$), and Ge_2O_5'' ($R = 1$) are formed as intermediate products of the depolymerisation process, it is evident from Table 2 that they can be adsorbed only over a short pH range, if at all. In fact, although salts such as $M_2Ge_4O_9$ and $M_2Ge_2O_5$ have been found in the systems Na_2O–GeO_2

and K_2O–GeO_2 (Schwarz and Heinrich, *Z. anorg. Chem.*, 1932, **205**, 43), no evidence seems yet to have been found for their existence in solution.

The ion-exchange data are consistent with the polymerisation of a monomeric species, possibly a monogermanic acid, to a pentagermanic acid, followed by a depolymerisation to a monogermanic acid again as the pH is raised. Although our data do not permit a distinction between the monogermanic acids formed at high and low pH values, yet Schwarz and Huf's molecular weight determinations (*loc. cit.*) suggest that they are not the same. The pentagermanate ion is evidently not too large to penetrate the resin pores, and the method we have employed should be suitable for studying other small polymeric ions and is in some ways complementary to that of Gustavson and Holm (*Svensk Kem. Tidskr.*, 1952, **64**, 137; cf. also Lister and Macdonald, *J.*, 1952, 4315).

The hydrolysis of the germanate form of the anion-exchanger suggests that the anion of a weak acid is adsorbed. At the same time it contrasts sharply with the strong adsorption of the pentagermanate ion in the presence of a five-fold greater concentration of chloride ion (*i.e.*, when the germanium and chloride concentrations are equal) at pH 9. A likely explanation would appear to be that, as the resin is brought from an alkaline medium to one of distilled water, the pentagermanate ion is hydrolysed to a monomeric form derived from the weaker monogermanic acid (cf. Carpeni, *loc. cit.*; $H_2Ge_5O_{11}$, $pK_1 = 6{\cdot}2$; H_2GeO_3, $pK_1 = 9{\cdot}1$). The weaker acid would then be readily removed from the resin by hydrolysis.

In the experiment where the resin, with both germanium and chloride adsorbed, was left in contact with a limited quantity of water, the amount of germanium left on the resin at equilibrium (Table 1) was close to that found to be adsorbed from a germanate solution of the same pH as the aqueous phase (Fig. 1). As this was on the alkaline side of the neutral point it is likely that some alkaline solution was entrained in the resin and that at a slightly lower pH the hydrolysis would have proceeded further.

It is apparent that there is little tendency for the germanate ions present to form complexes with chloride in solutions of the concentrations studied, and no evidence was found of the adsorption of any such complex ions.

The authors thank the Chemical Society and Imperial Chemical Industries Limited for grants.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, January 26th*, 1954.]

Products from the Alkaline and Reductive Fission of the Epoxide Ring of Methyl 3 : 4- and 2 : 3-Anhydro-6-deoxy-α-L-taloside and of their Methylated Derivatives.

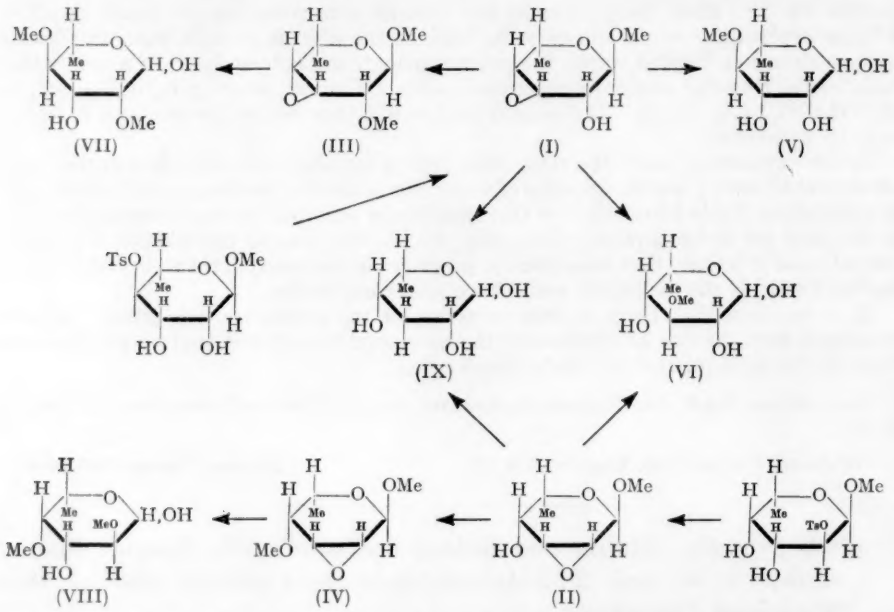
BY GEORGE CHARALAMBOUS AND ELIZABETH PERCIVAL.

[Reprint Order No. 5140.]

6-Deoxy-3-*O*-methyl-L-idose and 6-deoxy-4-*O*-methyl-L-mannose have been isolated from the alkaline fission of methyl 3 : 4-anhydro-6-deoxy-α-L-taloside. Methylation of the hydroxyl group at position 2, before fission, led to the isolation of 6-deoxy-2 : 4-di-*O*-methyl-L-mannose. Similar treatment of the 2 : 3-anhydro-derivatives gave rise to 6-deoxy-3-*O*-methyl-L-idose and 6-deoxy-2 : 4-di-*O*-methyl-L-galactose. Reduction of these epoxide ring compounds with lithium aluminium hydride afforded dideoxy-sugars.

PERCIVAL and ZOBRIST (*J.*, 1953, 564) examined the products of alkaline fission of methyl 2 : 3-anhydro-α-D-lyxoside and found that 2-*O*-methyl-D-xylose and 3-*O*-methyl-D-arabinose were obtained in the ratio of 1 : 2. However, if position 5 was substituted by a methoxyl radical then the only product isolated was 3 : 5-di-*O*-methyl-D-arabinose. These studies have now been extended to methyl 3 : 4- and 2 : 3-anhydro-6-deoxy-α-L-taloside and their methylated derivatives. Alkaline fission of the epoxide ring in methyl 3 : 4-anhydro-6-

deoxy-α-L-taloside (I) led to the isolation of 6-deoxy-4-*O*-methyl-L-mannose (4-*O*-methyl-L-rhamnose) (V) and 6-deoxy-3-*O*-methyl-L-idose (VI) in the ratio of approximately 1 : 2. The isolation of both possible fission products from the 3 : 4-anhydro-derivatives is in direct conformity with the results of Peat and Wiggins (*J.*, 1938, 1088), and of Percival and Zobrist (*loc. cit.*). On the other hand the 2 : 3-anhydro-derivative (II) gave only 6-deoxy-3-*O*-methyl-L-idose (VI) (70—80%) and 6-deoxy-L-idose (10—15%), there being no evidence for the presence of the other isomer, 6-deoxy-2-*O*-methyl-L-galactose (2-*O*-methyl-L-fucose), in the fission products. It is difficult to understand why only the deoxyidose derivative could be found, but steric factors may hinder the formation of the galactose derivative, as Gyr and Reichstein (*Helv. Chim. Acta*, 1945, **28**, 226) record the isolation of only the 3-*O*-methyl-D-idose derivative from methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-taloside, and Sorkin and Reichstein (*ibid.*, p. 1) the 2-*O*-methyl-D-idose derivative from methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-guloside.



6-Deoxy-3-*O*-methyl-L-idose has not been described previously and two identical fractions (1*a* and 1*b*), obtained respectively from the sodium methoxide fission of the epoxide ring of the 3 : 4- and the 2 : 3-anhydro-derivatives of talose, may presumably have this constitution as it is the only possible mono-*O*-methyl derivative which can be obtained by this means from both derivatives. Fischer, Bollinger, and Reichstein (*ibid.*, 1954, **37**, 6) have reported, since this work was completed, the synthesis of 6-deoxy-3-*O*-methyl-D-idose and its osazone. The constants recorded for these derivatives are the same (rotations of opposite sign) as those reported by us for the corresponding derivatives of the L-sugar.

From the methylated 3 : 4-anhydro- (III) and 2 : 3-anhydro- (IV) derivatives of talose only a single product was isolated: 6-deoxy-2 : 4-di-*O*-methyl-L-mannose (VII) from the former and 6-deoxy-2 : 4-di-*O*-methyl-L-galactose (VIII) from the latter. Butler, Lloyd, and Stacey (*Chem. and Ind.*, 1954, 107) have reported the synthesis of 6-deoxy-2 : 4-di-*O*-methyl-L-mannose by a different route, and our proof of the constitution of (VII) is based partly on the aniline derivative which is identical with the 6-deoxy-2 : 4-di-*O*-methyl-*N*-phenylmannosylamine synthesised by these authors, and partly on the fact that no evidence could be obtained for the presence of the other possible isomer, 6-deoxy-2 : 3-di-*O*-methyl-L-idose. Complete methylation of (VII) proved difficult and the syrupy trimethyl ether

isolated was contaminated with breakdown products as shown by its negative rotation and the poor yield of aniline derivative. However, oxidation of this ether, followed by esterification and amide formation, gave crystalline 2 : 3 : 4-tri-*O*-methyl-L-arabaramide, proving that the syrupy trimethyl ether was in fact mainly 6-deoxy-2 : 3 : 4-tri-*O*-methylmannose.

The isolation of the 6-deoxy-L-idose in greater quantity from the unmethylated 3 : 4-epoxide does not support the statement by Bose, Chaudhuri, and Bhattacharyya (*Chem. and Ind.*, 1953, 869) that " the opening of the 3 : 4-epoxide ring seems to follow the rule that the hydroxyl group at position 4 must be *trans* to the bulky primary hydroxyl group " while the isolation of 6-deoxy-2 : 4-di-*O*-methylmannose (VII) from the 2-methyl-3 : 4-epoxide (III) is in agreement with these authors' contention. It may well be, however, that the methyl group, which in the present experiments has replaced the primary hydroxyl group, has less influence on the scission of the epoxide ring. At the same time these authors, in an extension of Fürst and Plattner's rule (*12th Int. Cong. Pure and Appl. Chem.*, 1951, *Abs.*, p. 409), express the view that the predominant product from the scission of the epoxide ring in 2 : 3-anhydro-sugars has the entering group in the axial position, and the isolation of 6-deoxy-3-*O*-methyl-L-idose (VI) from methyl 2 : 3-anhydro-6-deoxy-α-L-taloside (II) is in direct support of this view. This is not true however for the product (VIII) from the fission of methyl 2 : 3-anhydro-6-deoxy-4-*O*-methyl-α-L-taloside (IV), the entering group being equatorial (C1 conformation). It appears that the presence of a methoxyl group in the molecule has a definite directing effect in the scission of the epoxide ring.

A syrup with similar rotations and the same R_G value was obtained from the action of lithium aluminium hydride on the methyl 3 : 4- and 2 : 3-anhydro-6-deoxy-α-L-talosides, (I) and (II). Consideration of the formulæ of these two substances makes it clear that the product must be 3 : 6-dideoxytalose (3 : 6-dideoxyidose) (IX). As the reduction product from the 3 : 4-anhydro-2-*O*-methyl derivative (III) on demethylation gave a syrup with the same R_G as (IX) it may be tentatively assumed that this product is the 3 : 6-dideoxy-2-*O*-methyltalose. No conclusions can be drawn, from the evidence obtained, of the constitution of the main product from the action of lithium aluminium hydride on the 2 : 3-anhydro-4-*O*-methyl derivative (IV).

Experimental

All solvents were removed under reduced pressure and below 50°. The R_G values were determined with *n*-butanol–ethanol–water (4 : 1 : 5).

Methyl 3 : 4-*Anhydro*-6-*deoxy*-α-L-*taloside* (I).—An ethanolic (50 ml.) solution of methyl 4-*O*-toluene-*p*-sulphonyl-α-L-rhamnoside (20·0 g., from 25 g. of rhamnose hydrate), prepared according to the method described by Percival and Percival (*J.*, 1950, 690), was titrated with sodium hydroxide (2M; 30·0 c.c.) at 75° until it was permanently pink to phenolphthalein. Sodium toluenesulphonate was filtered off, and the solution evaporated to dryness. Extraction of the residue with dry ethyl acetate (5 × 20 c.c.) at room temperature, removal of the solvent, and recrystallisation of the residue from warm light petroleum (b. p. 40—60°) gave crystalline *methyl* 3 : 4-*anhydro*-6-*deoxy*-α-L-*taloside* (I) (8·0 g.), m. p. 68°, $[\alpha]_D^{15}$ −110° (*c*, 1·1 in H_2O) (Found : C, 52·7; H, 7·4. $C_7H_{12}O_4$ requires C, 52·5; H, 7·5%).

Alkaline Hydrolysis of Methyl 3 : 4-*Anhydro*-6-*deoxy*-α-L-*taloside*.—(a) *With barium hydroxide.* Crystalline (I) (0·05 g.) was heated with barium hydroxide (1 g.) in water (5 c.c.) at 100° for 2 hr. After suitable treatment a syrup (0·025 g.), $[\alpha]_D^{14}$ −60° (*c*, 0·4 in H_2O), was obtained (cf. methyl 6-deoxy-α-L-mannoside, $[\alpha]_D^{16}$ −62° in H_2O). Hydrolysis with N-sulphuric acid gave a reducing syrup which partly crystallised when kept. The crystals had m. p. 91° alone and admixed with 6-deoxy-L-mannose. Examination of the mother liquors on a paper chromatogram showed two discrete spots, R_G 0·40 and 0·50, identical with those of 6-deoxy-L-mannose and 6-deoxy-L-idose which were run as controls. The 6-deoxy-L-mannose was present in much the larger quantity.

(b) *With sodium methoxide.* (I) (2·5 g.) was heated at 80° for 19 hr. with dry methanol (150 c.c.) containing sodium methoxide [from sodium (2·0 g.)]. The solution was neutralised with solid carbon dioxide and evaporated to dryness. Extraction with chloroform (6 × 50 c.c.) and removal of the solvent gave a mobile syrup (2·0 g.), b. p. 120—130°/0·1 mm., n_D^{12} 1·4685, $[\alpha]_D^{16}$ −117° (*c*, 2·0 in H_2O). This (1·2 g.) was hydrolysed at 100° with N-sulphuric acid (52 c.c.) until the rotation became constant ($[\alpha]_D^{15}$ −40°; 4 hr.). Neutralisation of the solution with barium carbonate and evaporation to dryness gave a syrup (1·02 g.). Examination on a paper chroma-

togram showed two discrete spots, R_G 0·75 and 0·66, together with faint spots which corresponded to 6-deoxyidose, R_G 0·50, and 6-deoxymannose, R_G 0·40. The mixture was separated by passage through cellulose (Chanda, Hirst, and Percival, *J.*, 1951, 1240). Elution was by purified light petroleum (b. p. 100—120°)–*n*-butanol (1 : 1; v/v) saturated with water. Fraction 1*a* was a syrup (0·575 g., 56·9%), R_G 0·75, M_G 0·80 (Consden and Stanier, *Nature*, 1952, **170**, 1069; Foster and Stacey, *J. Appl. Chem.*, 1953, **3**, 19), $[\alpha]_D^{16}$ −14° (*c*, 0·7 in H_2O), −13° (*c*, 1·0 in EtOH), n_D^{18} 1·4790 (Found: C, 47·8; H, 8·6; OMe, 18·0. Calc. for $C_7H_{14}O_5$: C, 47·1; H, 7·9; OMe, 17·4%). In one experiment, crystals (0·045 g.) were obtained; they had m. p. 113—114°, R_G 0·75, M_G 0·80, $[\alpha]_D^{17}$ +14·4° (*c*, 2·5 in EtOH), −15° (constant) (*c*, 1·0 in H_2O) (Found: C, 46·8; H, 7·95; OMe, 17·2%). Appropriate treatment of fraction 1*a* (0·065 g.) gave *6-deoxy-3-O-methyl-N-phenyl-*L*-idosylamine*, m. p. 62—63° (Found: C, 61·0; H, 8·0; N, 4·5. $C_{13}H_{19}O_4N$ requires C, 61·4; H, 7·9; N, 5·4%). Fraction 1*a* (30 mg.) in water (2 c.c.), phenylhydrazine (0·15 c.c.), and glacial acetic acid (2 drops) was heated at 100° for 2 hr. in an atmosphere of carbon dioxide. The solid obtained on cooling was recrystallised from aqueous ethanol, giving pale yellow needles of *6-deoxy-3-O-methyl-*L*-idosazone*, m. p. 122—123°, $[\alpha]_D^{16}$ −60° (*c*, 1·6 in EtOH) (Found: OMe, 8·4; N, 14·9. $C_{19}H_{24}O_3N_4$ requires OMe, 8·7; N, 15·8%). Fraction 2*a* was a syrup (0·270 g., 26·8%), R_G 0·66, which crystallised completely when kept; the solid had R_G 0·65, M_G 0·58, m. p. 122°, $[\alpha]_D^{15}$ +15° (*c*, 1·0 in MeOH) (Found: C, 47·2; H, 8·1; OMe, 17·2. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9; OMe, 17·4%). Levene and Muskat (*J. Biol. Chem.*, 1934, **105**, 431) record m. p. 122° and $[\alpha]_D$ +13° (in MeOH) for 6-deoxy-4-*O*-methylmannose. Fraction 3*a*, a syrup (0·051 g., 5·05%), had R_G 0·50, $[\alpha]_D^{16}$ −27·4° (*c*, 1·5 in H_2O). Meyer and Reichstein (*Helv. Chim. Acta*, 1946, **29**, 149) record $[\alpha]_D^{15}$ −26° (*c*, 4·462 in H_2O) for 6-deoxy-L-idose. Fraction 4*a* (0·060 g., 5·9%), R_G 0·40, crystallised completely and then had m. p. 92—94°, alone and mixed with authentic 6-deoxymannose.

Methyl 3 : 4-*Anhydro-6-deoxy-2-O-methyl-α-*L*-taloside* (III).—Crystalline methyl 3 : 4-anhydro-6-deoxy-α-L-taloside (I) (3·0 g.) was methylated four times with methyl iodide and silver oxide, and a mobile syrup (2·8 g.) was isolated, which distilled at 80—100°/0·01 mm. and had n_D^{15} 1·4500, $[\alpha]_D^{15}$ −140° (*c*, 0·6 in MeOH) (Found: OMe, 35·8. $C_8H_{14}O_4$ requires OMe, 35·6%).

Alkaline hydrolysis with sodium methoxide. Following the procedure used for the unmethylated material the syrup (III) (3·80 g.) was treated with sodium methoxide solution (250 c.c.). A mobile syrup (3·73 g.), $[\alpha]_D^{16}$ −60° (*c*, 1·0 in H_2O), was obtained. This was hydrolysed with N-sulphuric acid to constant rotation ($[\alpha]_D^{16}$ −12°; 3 hr.), and a syrup (*A*) (3·2 g.) which partly crystallised on storage at 0° was obtained. The crystals (VII) (1·17 g.) had m. p. 82°, $[\alpha]_D^{16}$ −19° (*c*, 1·0 in H_2O), +14·5° ⟶ −3° (48 hr. constant) (*c*, 1·8 in EtOH) (Found: C, 49·5; H, 8·1; OMe, 31·7. Calc. for $C_8H_{16}O_5$: C, 49·9; H, 8·4; OMe, 32·3%). The mother liquors (2·03 g.) from (*A*) on chromatographic analysis showed a main spot, R_G 0·86, and a fainter spot, R_G 1·0. Purification, by passage through powdered cellulose as described previously, gave a further yield of crystals (VII) (0·8 g.), m. p. 82°, a residual syrup (*B*), R_G 0·86, (0·81 g.), and a small quantity of a second fraction, R_G 1·0, $[\alpha]_D$ +20° (*c*, 0·05 in H_2O).

Characterisation of 6-Deoxy-2 : 4-di-O-methylmannose.—The crystals (VII) (0·05 g.) were demethylated by hydriodic acid (2 c.c.) at 100° for 10 min. A syrup which on chromatographic analysis gave a single spot identical with that given by 6-deoxymannose was isolated. Demethylation of syrup (*B*) which was chromatographically and ionophoretically identical with the crystals (VII) gave rise to a similar syrup which revealed only the presence of 6-deoxymannose.

The crystals (VII) (100 mg.) were oxidised with bromine water (1 c.c.) at 15° for 96 hr. The lactone (75 mg.), isolated in the usual way, had $[\alpha]_D^{15}$ +47° (*c*, 0·9 in H_2O) unchanged after 70 hr.; it failed to crystallise or to yield a crystalline amide or phenylhydrazide.

The crystals (VII) (0·1 g.) were heated at 80° for 6 hr. with ethanol (6 c.c.) containing aniline (0·55 c.c.) in the presence of Drierite (0·2 g.). Removal of the solvent at room temperatures gave 6-deoxy-2 : 4-di-*O*-methyl-*N*-phenylmannosylamine, m. p. 141—142°, $[\alpha]_D^{16}$ +110° ⟶ +7° (20 hr.) (*c*, 0·4 in EtOH) (Found: C, 60·8; H, 7·5; OMe, 23·3; N, 5·4. Calc. for $C_{14}H_{21}O_4N$: C, 62·9; H, 7·9; OMe, 23·2; N, 5·2%). An *X*-ray powder photograph of this aniline derivative obtained through the courtesy of Dr. C. A. Beevers was pronounced identical with one of 6-deoxy-2 : 4-di-*O*-methyl-*N*-phenylmannosylamine synthesised in the Birmingham laboratories and supplied by Professor M. Stacey, F.R.S. (*Chem. and Ind.*, 1954, 107). The residual syrup (*B*) gave an identical aniline derivative, m. p. 141—142° alone and mixed with the derivative prepared from the crystals.

The dimethyl sugar (VII) (0·165 g.) was converted into the glycoside (0·150 g.) with 1%-methanolic hydrogen chloride, and this was followed by four methylations with methyl iodide

and silver oxide. A mobile syrup (0·145 g.), n_D^{16} 1·4421, $[\alpha]_D^{16}$ −17° (*c*, 1·5 in H_2O), was isolated. Hirst and Macbeth (*J.*, 1926, 22) record n_D^{15} 1·4423, $[\alpha]_D^{16}$ −15° (in H_2O), for methyl 6-deoxy-2 : 3 : 4-tri-*O*-methyl-L-mannoside (Found : OMe, 55·6. Calc. for $C_{10}H_{20}O_4$: OMe, 56·3%). Hydrolysis with N-sulphuric acid gave a syrup, $[\alpha]_D^{17}$ −12° (*c*, 0·5 in H_2O), −24° (*c*, 0·8 in EtOH) {Hirst and Macbeth, *loc. cit.*, record $[\alpha]_D$ +25° (in H_2O), −9° (in ethanol), for 6-deoxy-2 : 3 : 4-tri-*O*-methyl-L-mannose}, which on chromatographic analysis gave a single discrete spot (R_G 1·01) identical with the spot given by authentic 6-deoxy-2 : 3 : 4-tri-*O*-methyl-L-mannose. Attempted conversion into 6-deoxy-2 : 3 : 4-tri-*O*-methyl-*N*-phenylmannosylamine gave a very poor yield of crystals, m. p. and mixed m. p. 111—112°.

Oxidation of the trimethyl ether (0·30 g.) with nitric acid (5·5 c.c.; *d*, 1·42) (Mullan and Percival, *J.*, 1940, 1505) gave a syrup (0·06 g.) which was esterified with boiling methanolic hydrogen chloride (2%; 3·5 c.c.) for 6 hr. The derived amide, $[\alpha]_D^{16}$ +52° (*c*, 0·5 in EtOH), partly crystallised, m. p. and mixed m. p. 230°. Hirst and Macbeth (*loc. cit.*) record $[\alpha]_D^{16}$ +50·4° (in H_2O) for 2 : 3 : 4-tri-*O*-methyl-L-arabaramide.

Methyl 2 : 3-*Anhydro*-6-*deoxy*-α-L-*taloside* (II).—Crystalline methyl 6-deoxy-2-*O*-toluene-*p*-sulphonyl-α-L-galactoside (3·30 g.), prepared from 6-deoxygalactose by Percival and Percival's method (*loc. cit.*), was titrated with sodium hydroxide (2M; 9 c.c.) as described for the corresponding 6-deoxymannose derivative. Removal of ethyl acetate gave an extremely volatile crystalline product (II) (1·70 g.) which after recrystallisation from ethanol had m. p. 95—97°, $[\alpha]_D^{16}$ −88° (*c*, 2·0 in H_2O) (Found : C, 52·45; H, 7·3. $C_7H_{12}O_4$ requires C, 52·5; H, 7·5%). This *taloside* was very soluble in alcohol, acetone, chloroform, and light petroleum.

Alkaline hydrolysis. Hydrolysis of (II) with sodium methoxide as described above gave a syrup (0·32 g. from 0·35 g.). Removal of the glycosidic group with N-sulphuric acid afforded a syrup (*C*) (0·21 g.) which on chromatographic analysis showed two spots, R_G 0·75 and 0·50. Separation on cellulose gave two fractions. Fraction 1*b* was a syrup (0·150 g.), $[\alpha]_D^{16}$ −14° (*c*, 0·7 in H_2O) (Found : OMe, 17·5. Calc. for $C_7H_{14}O_5$: OMe, 17·4%), which was chromatographically and ionophoretically identical with fraction I*a*, obtained by similar treatment of the 3 : 4-anhydro-derivative. 6-Deoxy-3-*O*-methyl-*N*-phenyl-L-idosylamine, m. p. and mixed m. p. 62—63°, and 6-deoxy-3-*O*-methyl-*N*-phenyl-L-idosazone, m. p. and mixed m. p. 122—123°, were also prepared from fraction I*b*. Fraction 2*b*, a syrup (0·030 g.; 15%), $[\alpha]_D^{16}$ −22° (*c*, 1·0 in H_2O), R_G 0·50, was presumed to be 6-deoxy-2-*O*-methylgalactose. Nucleation, however, failed to induce crystallisation, and chromatographic comparison showed that authentic 6-deoxy-2-*O*-methylgalactose has R_G 0·59. Paper ionophoresis of 6-deoxy-2-*O*-methylgalactose gave M_G 0·33 while fraction 2*b* gave M_G 1·0 and 6-deoxygalactose 0·92. 6-Deoxy-L-idose (fraction 3*a*) had R_G 0·59, M_G 1·0.

Methyl 2 : 3-*Anhydro*-6-*deoxy*-4-O-*methyl*-α-L-*taloside* (IV).—(II) (1·01 g.) was methylated four times with methyl iodide and silver oxide. Recrystallisation of the *taloside* (IV) from acetone–light petroleum (b. p. 40—60°) gave long needles, m. p. 108—110°, $[\alpha]_D^{16}$ ±0° (*c*, 0·7 in EtOH, $CHCl_3$, and $COMe_2$) (Found : C, 54·7; H, 8·1; OMe, 35·0. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1; OMe, 35·6%).

Alkaline hydrolysis. Methyl 2 : 3-anhydro-6-deoxy-4-*O*-methyl-α-L-taloside (IV) (0·90 g.) was hydrolysed with sodium methoxide as described for the 3 : 4-anhydro-derivative. The resultant syrup (0·70 g.) after hydrolysis with sulphuric acid had $[\alpha]_D^{18}$ −15° (*c*, 2·4 in MeOH) and gave, on chromatographic analysis, a single spot R_G 0·80 (Found : OMe, 31·8. $C_8H_{16}O_5$ requires OMe, 32·3%).

Characterisation of the syrupy dimethyl compound, R_G 0·80. Demethylation of a portion (0·050 g.) of the syrup with hydriodic acid (*d*, 1·7; 2 c.c.) gave a product which was chromatographically indistinguishable from 6-deoxy-L-galactose.

The syrup, R_G 0·80 (0·235 g.), was converted into the glucoside by methanolic hydrogen chloride (2%; 24 c.c.) at 80°, until it did not reduce Fehling's solution (3 hr.). The glycoside, $[\alpha]_D^{16}$ −30° (*c*, 1·5 in EtOH), was methylated five times with methyl iodide and silver oxide; the resultant methyl tri-*O*-methylglycoside crystallised spontaneously. The crystals (0·15 g.) had m. p. and mixed m. p. 93—95°, $[\alpha]_D^{16}$ −200° (*c*, 1·0 in H_2O) (Found : C, 54·05; H, 9·1; OMe, 55·4. Calc. for $C_{10}H_{20}O_5$: C, 54·55; H, 9·1; OMe, 56·3%) [James and Smith, *J.*, 1945, 746, record m. p. 85—92°, $[\alpha]_D$ −196° (*c*, 0·5 in H_2O), for methyl 6-deoxy-2 : 3 : 4-tri-*O*-methyl-α-L-galactoside.]

Dideoxy-sugars derived by the Action of Lithium Aluminium Hydride on Methyl Anhydro-6-deoxytalosides.—Each of the above anhydro-derivatives (I—IV) was treated with lithium aluminium hydride, and the products examined chromatographically. All attempts to prepare crystalline aniline derivatives, phenylosazones, and toluene-*p*-sulphonyl derivatives failed.

A typical reduction was carried out as follows. Crystalline methyl 3 : 4-anhydro-6-deoxy-α-L-taloside (I) (2·0 g.) in dry ether (150 c.c.) was added dropwise during 45 min. to a gently refluxing suspension of finely powdered lithium aluminium hydride (2·0 g.) in dry ether (150 c.c.) under vigorous stirring, and the reaction allowed to continue a further 4 hr. The flask was cooled in ice-water, excess of lithium aluminium hydride destroyed by the careful addition of water, and the mixture made acid (2N-sulphuric acid). Exhaustive extraction with chloroform (10 × 100 c.c.) afforded, after purification with Filter Cel, a syrup (0·7 g.) which was hydrolysed with N-sulphuric acid; the resultant reducing syrup showed a single discrete spot on chromatographic analysis.

Similar treatment of the other anhydro-derivatives (II—IV) gave syrups contaminated with 6-deoxy-idose and -galactose and separation on cellulose was necessary. In addition the methylated anhydro-sugars (III) and (IV) also gave some of the products isolated from (I) and (II). The constants of the main products after separation were:

Product from methyl 6-deoxy-α-L-taloside	Yield, %	$[\alpha]_D^{16}$ in MeOH	$[\alpha]_D^{16}$ in H_2O	OMe, %	R_G
3 : 4-Anhydro-	38	−20°	−16°	—	0·72
2 : 3-Anhydro-	11	−18	−20	—	0·72
3 : 4-Anhydro-2-*O*-methyl-	17	−14	− 4	19·2	0·90
2 : 3-Anhydro-4-*O*-methyl-	20	−25	−38	18·7	0·93

Demethylation of the syrup, R_G 0·90, gave a chromatographically pure syrup, R_G 0·72.

Application of the Dische test (Dische, *Mikrochem.*, 1930, **8**, 4; Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222), as extended by Allerton, Overend, and Stacey (*J.*, 1952, 255) to 3-deoxyxylose and 2 : 3-dideoxyribose, to these dideoxy-derivatives gave values for the molecular extinction coefficients which were in reasonable agreement with those obtained by the last authors.

The authors are very grateful to Professor E. L. Hirst, F.R.S., for his interest and advice. Thanks are expressed to Imperial Chemical Industries Limited and to the Distillers Company Limited for grants.

Department of Chemistry,
University of Edinburgh.

[*Received, February 22nd*, 1954.]

Antimalarial 2-Alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes.

By D. M. Besly and A. A. Goldberg.

[Reprint Order No. 5181.]

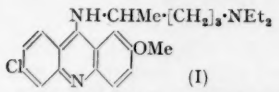
2-Alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes have been synthesised because of their structural relation to mepacrine and pamaquine. One of these, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene dihydrochloride ("Azacrin"), is highly active against human malaria due to *P. falciparum* and *P. vivax*.

Condensation of 2-alkoxy-5-aminopyridines with 2 : 4-dichlorobenzoic acid gave 2-(6-alkoxy-3-pyridylamino)-4-chlorobenzoic acids. Cyclisation with phosphoryl chloride yielded 2-alkoxy-6 : 9-dichloro-1 : 10-diaza-anthracenes which reacted with dialkylaminoalkylamines to give the desired compounds.

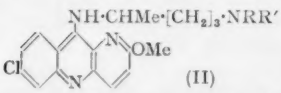
Observations have been made upon the failure of *o*-3-pyridylaminobenzoic acids to cyclise unless the pyridine ring contains an electron-releasing substituent. It has been proved by rational synthesis that ring closure takes place on the 2-position of the pyridine ring.

Analogues (II) of mepacrine (I) derived from 1 : 10-diaza-anthracene were required for examination for antiplasmodial activity because they bear structural resemblance to pamaquine (III; R ≐ R′ = Et) inasmuch as the dialkylaminoalkylamino-side-chain is *peri* to a ring-nitrogen atom. Pamaquine and primaquine (III; R = R′ = H) are the most effective of the known antimalarials against the secondary exoerythrocytic stages of the parasite

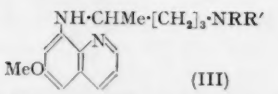
responsible for relapse in infections due to *P. vivax* (Report by Council on Pharmacy & Chemistry, *J. Amer. Med. Assoc.*, 1952, **149**, 1558); the possibility was envisaged that compounds of type (II) might combine the schizonticidal activity of mepacrine with the radically curative properties of pamaquine. A further point of interest arises from the hypothesis (Madinaveitia, *Biochem. J.* 1946, **40**, 373) that antimalarials function by virtue of their ability to antagonise riboflavine, an essential factor for the survival of the plasmodium. 1 : 10-Diaza-anthracenes of type (II) are more closely related to riboflavine than is mepacrine and might therefore be expected to be superior flavin antagonists.



(I)



(II)



(III)

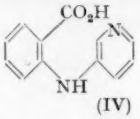
Previous attempts to prepare 9-dialkylaminoalkylamino-diaza-anthracenes from *o*-pyridylaminobenzoic and 3-phenylaminopicolinic acids have been unsuccessful (Kermack and Wetherhead, *J.*, 1942, 726; Petrov, *J.*, 1945, 927; 1949, 1157; Price and Roberts, *J. Org. Chem.*, 1946, **11**, 463; Bachmann and Barker, *ibid.*, 1949, **14**, 97); in the few instances where ring closure was accomplished, trans-annular tautomerism of the central ring was inhibited and the 9-chlorodiaza-anthracene, essential for introduction of the dialkylaminoalkylamino-side-chain, was unobtainable. The present communication records the synthesis of a number of 2-alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes and related compounds.

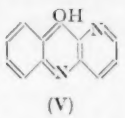
Condensation of 5-amino-2-methoxypyridine with 2 : 4-dichlorobenzoic acid gave 4-chloro-2-(6-methoxy-3-pyridylamino)benzoic acid. The Ullmann condensation between an *o*-chlorobenzoic acid and an arylamine is normally effected in presence of a considerable excess of potassium carbonate which functions as acid acceptor for the hydrogen chloride eliminated. During the latter part of the work it was observed that better yields were obtained by use of 0·5 mole of potassium carbonate for each mole of the *o*-chlorobenzoic acid, less tar being formed by alkaline decomposition of the pyridylamine. Under these conditions the condensation is essentially a reaction between the potassium *o*-chlorobenzoate and the pyridylamine in the absence of an inorganic acid acceptor: the potassium *o*-pyridylaminobenzoate, as it is formed, acts as acid acceptor by virtue of the fact that *o*-pyridylaminobenzoic acids have considerably higher pK_a values than the *o*-chlorobenzoic acids. At termination, the reaction mixture has pH *ca.* 4; that the reaction takes place at this pH conforms with the suggestion (Goldberg, *J.*, 1953, 4368) that it proceeds *via* a copper chelate complex and only in an environment which allows this to exist, since a number of well-known copper chelate compounds, including copper acetylacetone, are stable in boiling amyl alcohol–acetic acid solution. Cyclodehydration of 4-chloro-2-(6-methoxy-3-pyridylamino)benzoic acid by Magidson and Grigowski's method (*Ber.*, 1933, **66**, 866) yielded 6 : 9-dichloro-2-methoxy-1 : 10-diaza-anthracene which, when heated in phenol with 4-diethylamino-1-methylbutylamine, was converted into 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene, conveniently isolated as the dihydrochloride. By the above synthetic procedure, using various 2-alkoxy-5-aminopyridines, substituted *o*-chlorobenzoic acids and dialkylaminoalkylamines, a number of 2-alkoxy-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes bearing substituents in the 6- and the 7-position have been prepared and screened for activity against *P. gallinaceum* and *P. berghei* infections in chicks and mice respectively.

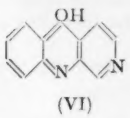
Treatment of *o*-(6-benzyloxy-3-pyridylamino)benzoic acids with phosphoryl chloride effected cyclisation and simultaneous chlorinolysis of the benzyloxy-group with production of 2 : 9-dichloro-1 : 10-diaza-anthracenes. These are of interest because the difference in reactivity of the halogen substituents permits their stepwise replacement with any desired amine; the 2-chloro-atom has the comparatively low mobility associated with that in 2-chloropyridine and the 9-chloro-atom the high reactivity of the halogen in 5-chloroacridine.

The Cyclisation of o-3-*Pyridylaminobenzoic Acids.*—*o*-3-Pyridylaminobenzoic acids (IV) may give rise to the 9-hydroxy- or the 9-chloro-derivative of 1 : 10- (V) or 3 : 10-diaza-anthracene (VI) according to whether cyclisation proceeds upon the 2- or the 4-position of

the pyridine ring. Similar types of cyclodehydration occur with 2-carboxy-3′-nitrodiphenylamines which cyclise principally upon the 2′-position (Goldberg and Kelly, *J.*, 1946, 103; cf. the ring closure of 2-carboxy-3′-nitrodiphenyl ethers upon the 2′-position; Goldberg and Walker, *J.*, 1953, 1348). The striking similarity between the substitution reactions of pyridine and nitrobenzene (Elderfield, "Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, pp. 408 *et seq.*) suggests that *o*-3-pyridylaminobenzoic acids would similarly

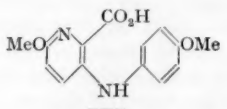

(IV)

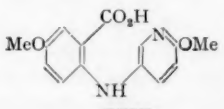

(V)

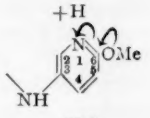

(VI)

cyclise upon the 2-position of the pyridine ring and this is supported by the fact that, in compounds of type (IV), ability to cyclise is suppressed by blockage of the 2- but not of the 4-position: 4-chloro-2-(6-methoxy-4-methyl-3-pyridylamino)benzoic acid is, and 4-chloro-2-(6-methoxy-2-methyl-3-pyridylamino)benzoic acid is not, cyclodehydrated by sulphuric acid or phosphoryl chloride.

Cyclodehydration of *o*-3-pyridylaminobenzoic acids in strong acid comprises the initial protonisation of the carbonyl oxygen followed by the attack of the carbonium ion on the pyridine nucleus. The reaction will proceed if the electron density at the available points for ring closure ($C_{(2)}$ and $C_{(4)}$ of the pyridine ring) is sufficiently high, its direction being governed by the relative electron densities. With regard to the direction it is significant that the total mobile electron densities computed by the method of molecular orbitals (Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87) at the 2-position in pyridine is considerably higher than it is at the 4-position; this must also be the case with 3-aminopyridine which is chlorinated in acid (Schick, Binz, and Schultz, *Ber.*, 1936, **69**, 2593) and sulphonated (Plazek, *Roczn. Chem.*, 1937, **17**, 97), and undergoes the Skraup cyclisation (Klisiecki and Sucharda, *ibid.*, 1927, **7**, 204; Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081), exclusively at the 2-position. The electromeric shift induced by the 6-alkoxy-group cannot assist the electron distribution at either $C_{(2)}$ or $C_{(4)}$ of the pyridine ring; it would therefore be expected that 2-(6-alkoxy-3-pyridylamino)benzoic acid would cyclise upon the 2-position of the pyridine ring. That this is the case has been shown by rational synthesis of a typical compound of the series. 3-Chloro-6-methoxypicolinic acid was condensed with *p*-anisidine; the product (VII) cyclised with phosphoryl chloride to 9-chloro-2 : 7-dimethoxy-1 : 10-diaza-anthracene identical with the product obtained by ring closure of 5-methoxy-2-(6-methoxy-3-pyridylamino)benzoic acid (VIII).


(VII)


(VIII)


(IX)

The failure of unsubstituted *o*-3-pyridylaminobenzoic acids to cyclise requires comment in view of the facility with which *o*-3-nitroanilinobenzoic acids undergo ring closure. Consideration of the electrophilic and nucleophilic substitution reactions of pyridine and nitrobenzene in acid media indicates that the $-I$ effect of the protonised nitrogen of the former is considerably more powerful than that of the nitro-group in the latter, their $-T$ effects being of a comparable order. It is therefore not surprising that the electron density at the 2- and the 4-position in the pyridine ring in an unsubstituted *o*-3-pyridylaminobenzoic acid should be below the threshold value required for cyclisation. The $+T$ effect of an alkoxy-group is greater than the combined $-I$ and $-T$ effects of the pyridine-nitrogen atom as shown by the ease with which 3-alkoxypyridines are nitrated at the 2-position (den Hertzog, *Rec. Trav. chim.*, 1949, **68**, 275). In a 2-(6-methoxy-3-pyridylamino)benzoic acid the electromeric effect of the alkoxy-group cannot *directly* affect the electron density at the 2- and the 4-position of the pyridine ring although the mesomerism of the protonised cyclic

imino-ether (IX) may cause partial bond fixation and suppress the inductive and tautomeric mechanisms by which the nitrogen atom normally creates electron defect at $C_{(2)}$ and $C_{(4)}$. Cyclisation would in consequence proceed at $C_{(2)}$ since ring closure can only take place across a double bond (cf. Lellmann and Schmidt, *Ber.*, 1887, **20**, 3154; Markwald, *Annalen*, 1894, **279**, 1).

Chemotherapeutic Activity.—6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene dihydrochloride (" Azacrin ") at an oral dosage of 25 mg./kg. per day gives the same effective control of *P. gallinaceum* infections in chicks as 50 mg./kg. per day of mepacrine, or 12·5 mg./kg. of chloroquine; in mice, 5 mg./kg. of " Azacrin " (LD_{50} = 900 mg./kg.) per day has the same suppressive activity as 5 mg./kg. per day of mepacrine (LD_{50} = 850 mg./kg.) or 3·0 mg./kg. of chloroquine (LD_{50} = 400 mg./kg.). Making use of these results Bruce-Chwatt and Archibald (*Brit. Med. J.*, 1953, I, 539) and Ang'awa and Fendall (*J. Trop. Med. Hyg.*, 1954, **57**, 59) have found " Azacrin " to be a very effective schizonticide in human malaria due to *P. falciparum*, having shorter pyrexia- and parasite-clearance times, and allowing fewer relapses, than mepacrine.

Experimental

Substituted 3-aminopyridines

The 2-alkoxy-5-aminopyridines were obtained from 2-chloro-5-nitropyridine (Caldwell and Kornfield, *J. Amer. Chem. Soc.*, 1942, **64**, 1696) and the sodium alkoxide, the nitroalkoxypyridine then being reduced with iron powder (Friedman, Braitberg, Tolstoouhov, and Tizsa, *ibid.*, 1947, **69**, 1204). The overall yield from 2-aminopyridine was in each case *ca.* 40%. 5-Amino-2-methoxypyridine had b. p. 98—102°/3 mm., 5-amino-2-*n*-butoxypyridine b. p. 128—130°/2 mm., 5-amino-2-benzyloxypyridine m. p. 46—48°, and 5-amino-2-phenoxypyridine m. p. 70—72°.

2-*Amino*-4-*methyl*-5-*nitropyridine*.—Nitration of 2-amino-4-methylpyridine (40 g.) by Seide's method (*Ber.*, 1924, **57**, 791) gave non-volatile 2-amino-4-methyl-5-nitropyridine (30 g.), m. p. 220—222°, and the steam-volatile 3-nitro-isomer (11 g.), m. p. 140°.

2-*Hydroxy*-4-*methyl*-5-*nitropyridine*.—To a solution of 2-amino-4-methyl-5-nitropyridine (17·4 g.) in water (300 c.c.) and sulphuric acid (30 c.c.; *d* 1·84), stirred at 10—15°, was added dropwise sodium nitrite (17·5 g.) in water (35 c.c.); the mixture was stirred a further 2 hr. at room temperature, then raised cautiously (frothing) to the b. p. and then chilled in ice water. The precipitate, on crystallisation from water (*ca.* 200 c.c.), gave 2-*hydroxy*-4-*methyl*-5-*nitropyridine* (15 g.) as orange plates, m. p. 186—188° (Found: N, 18·0. $C_6H_6O_3N_2$ requires N, 18·2%).

2-*Chloro*-4-*methyl*-5-*nitropyridine*.—The foregoing compound (19·8 g.) was refluxed for 4 hr. with phosphorus pentachloride (27 g.) and phosphoryl chloride (5 c.c.). Excess of phosphoryl chloride was distilled off at reduced pressure, the residue quenched on ice, and the sticky product drained on porous tile. The air-dried material, mixed with charcoal, was extracted with ligroin (b. p. 40—60°) (Soxhlet). On cooling of the ligroin liquors, 2-*chloro*-4-*methyl*-5-*nitropyridine* (16·4 g.) separated as yellow prisms, m. p. 40—44° (Found: N, 16·6; Cl, 20·8. $C_6H_5O_2N_2Cl$ requires N, 16·2; Cl, 20·6%).

2-*Methoxy*-4-*methyl*-5-*nitropyridine*.—The foregoing compound (15 g.) was added portionwise to a solution of sodium (2·1 g.) in anhydrous methanol (100 c.c.). Next morning the mixture was refluxed for ½ hr., then poured on ice (800 g.), and the 2-*methoxy*-4-*methyl*-5-*nitropyridine* (13·8 g.; m. p. 80—84°) collected and dried at 30°; a sample crystallised from ligroin (b. p. 60—80°) in needles, m. p. 82—84° (Found: N, 17·1. $C_7H_8O_3N_2$ requires N, 16·7%).

5-*Amino*-2-*methoxy*-4-*methylpyridine*.—The foregoing nitro-compound (13·6 g.) was added portionwise during 45 min. to a stirred, refluxing mixture of water (100 c.c.), alcohol (100 c.c.), acetic acid (2 c.c.), and Pacteron iron dust (33 g.). After a further 2 hours' stirring at the b. p., potassium hydrogen carbonate (50 g.) was cautiously added, the mixture stirred at the b. p. for a further 3 hr., and the iron oxide filtered off and washed with boiling alcohol (250 c.c.). The combined filtrates were concentrated almost to dryness at reduced pressure, the residue was extracted with ether (3 × 100 c.c.), and the ethereal solution dried (K_2CO_3). Distillation of the ether left the *product* (10 g.) as a mass of needles, m. p. 94—96°; a sample separated from ligroin (b. p. 60—80°) in needles, m. p. 97° (Found: N, 20·1. $C_7H_{10}ON_2$ requires N, 20·3%).

5-*Amino*-2-*methoxy*-6-*methylpyridine*.—Nitration of 2-amino-6-methylpyridine (50 g.) by Parker and Schine's method (*J. Amer. Chem. Soc.*, 1947, **69**, 63) and crystallisation of the non-volatile product twice from boiling water (130 c.c./g.) yielded 2-amino-6-methyl-5-nitropyridine

(31 g.), m. p. 190°, pure enough for the next stage. (The amount of steam-volatile 3-nitro-isomer obtained was 16 g., having m. p. 156—158°.) The 5-nitro-compound was converted into the amine as described above. The intermediate compounds thus obtained and the yields were: 2-hydroxy-6-methyl-5-nitro- (95%), m. p. 234—236°, 2-chloro-6-methyl-5-nitro- (96%), m. p. 55°, 2-*methoxy*-6-*methyl*-5-*nitro*- (93%), m. p. 70—72° (Found: N, 17·1. $C_7H_8O_3N_2$ requires N, 16·7%), and 5-*amino*-2-*methoxy*-6-*methyl-pyridine* (75%), b. p. 97°/1 mm. (Found: N, 19·9. $C_7H_{10}ON_2$ requires N, 20·3%).

o-3-*Pyridylaminobenzoic acids*

General Procedure.—The *o*-chlorobenzoic acid (0·1 mole) was dissolved in amyl alcohol (100 c.c.) in a 3-necked flask and stirred at *ca.* 100° for ½ hr. with the copper catalyst and anhydrous potassium carbonate (0·05—0·125 mole) in order to obtain the potassium salt in a voluminous state. The aminopyridine (0·1 mole) was added and the mixture stirred at the b. p. for the stated time; water formed was removed by a Dean and Stark apparatus. The mixture was poured into water and basified (if necessary) with potassium carbonate, the amyl alcohol removed in steam, and the residual aqueous liquor filtered from tar. Acidification to pH 6·5 frequently precipitated more tar; after removal of this with charcoal the solution was stirred at *ca.* 80°, and adjusted to pH 4 by addition of hydrochloric acid. The precipitated *o*-pyridylaminobenzoic acid was collected and washed with boiling water to remove unchanged starting material.

4-*Chloro*-2-(6-*methoxy*-3-*pyridylamino*)*benzoic Acid.*—2 : 4-Dichlorobenzoic acid (19·1 g.), anhydrous potassium carbonate (6·9 g.), copper oxide (0·1 g.), 5-amino-2-methoxypyridine (13 g.), and amyl alcohol (100 c.c.) gave, in 3 hr., the crude product as a bluish white powder (19 g., 68%); the pure *acid* separated from ethanol or ethyl methyl ketone in almost colourless needles, m. p. 208° (Found: equiv., 278; N, 10·1; Cl, 12·7%. $C_{13}H_{11}O_3N_2Cl$ requires equiv., 278·5; N, 10·1; Cl, 12·75%).

2-(6-n-*Butoxy*-3-*pyridylamino*)-4-*chlorobenzoic Acid.*—2 : 4-Dichlorobenzoic acid (19·1 g.), potassium carbonate (17·25 g.), 5-amino-2-*n*-butoxypyridine (20·8 g.), copper oxide (0·5 g.) and cuprous iodide (0·5 g.), in amyl alcohol (300 c.c.) at 132° for 3 hr., gave the required *acid* in buff crystals (11 g.), m. p. 148° (from aqueous methanol) (Found: equiv., 319; N, 9·0; Cl, 11·0%. $C_{16}H_{17}O_3N_2Cl$ requires equiv., 320·5; N, 8·7; Cl, 11·1%).

4-*Chloro*-2-(6-*phenoxy*-3-*pyridylamino*)*benzoic Acid.*—2 : 4-Dichlorobenzoic acid (14 g.), potassium carbonate (10·5 g.), cupric oxide (0·1 g.), 5-amino-2-phenoxypyridine (9·3 g.), and amyl alcohol (50 c.c.) in 10 hr. gave a light brown tar which solidified under 60% acetic acid; recrystallisation from methanol or toluene gave the pure colourless *acid* (2·3 g.), m. p. 186—188° (Found: equiv., 342; N, 8·3; Cl, 10·4%. $C_{18}H_{13}O_3N_2Cl$ requires equiv., 340·5; N, 8·2; Cl, 10·4%).

4-*Chloro*-2-(6-*benzyloxy*-3-*pyridylamino*)*benzoic Acid.*—2 : 4-Dichlorobenzoic acid (24 g.), potassium carbonate (20 g.), copper oxide (0·25 g.), amyl alcohol (100 c.c.), and 5-amino-2-benzyloxypyridine (20 g.) were stirred for 3 hr. The glutinous crude product was triturated with cold alcohol (100 c.c.) and the residual solid crystallised from boiling alcohol to give the pure *acid* in colourless needles (5·4 g.), m. p. 188—190° (Found: equiv., 349; N, 8·2; Cl, 10·1%. $C_{19}H_{15}O_3N_2Cl$ requires equiv., 354·5; N, 7·9; Cl, 10·0%).

5-*Chloro*-2-(6-*benzyloxy*-3-*pyridylamino*)*benzoic Acid.*—2 : 5-Dichlorobenzoic acid (24 g.), potassium carbonate (18 g.), copper oxide (0·25 g.), amyl alcohol (100 c.c.), and 5-amino-2-benzyloxypyridine (20 g.) (3 hr.) gave a glutinous crude product. Trituration with cold methanol (100 c.c.) and crystallisation from dilute acetic acid gave the pure *acid* as grey needles (20 g.), m. p. 222° (Found: equiv., 348; N, 8·0; Cl, 9·9%. $C_{19}H_{15}O_3N_2Cl$ requires equiv., 354·5; N, 7·9; Cl, 10·0%).

5-*Methoxy*-2-(6-*methoxy*-3-*pyridylamino*)*benzoic Acid.*—Boiling 2-chloro-5-methoxybenzoic acid (28 g.), potassium carbonate (21 g.), amyl alcohol (100 c.c.), cupric oxide (0·25 g.), and 5-amino-2-methoxypyridine (14·8 g.) for 4 hr. gave a pale yellow *acid* (6 g.), m. p. 190—192° (from alcohol) (Found: equiv., 278; N, 10·3%. $C_{14}H_{14}O_4N_2$ requires equiv., 274; N, 10·2%).

2-(6-*Benzyloxy*-3-*pyridylamino*)*benzoic Acid.*—*o*-Chlorobenzoic acid (49 g.), potassium carbonate (45 g.), copper oxide (0·25 g.), cuprous iodide (0·25 g.), amyl alcohol (250 c.c.), and 5-amino-2-benzyloxypyridine (48 g.) (7 hr.) gave a semi-solid *product* which, when washed with cold alcohol and then toluene, and crystallised from alcohol had m. p. 178—180° (45 g.) (Found: equiv., 320; N, 8·8%. $C_{19}H_{16}O_3N_2$ requires equiv., 320; N, 8·75%).

4-*Chloro*-2-(6-*methoxy*-4-*methyl*-3-*pyridylamino*)*benzoic Acid.*—2 : 4-Dichlorobenzoic acid (8·8 g.), potassium carbonate (3·25 g.), 5-amino-2-methoxy-4-methylpyridine (6·4 g.), amyl alcohol

(50 c.c.), and traces of copper bronze and cuprous iodide (5 hr.) gave the *acid* (5 g.), as needles (from alcohol), m. p. 250—252° (Found: equiv., 293; N, 9·8; Cl, 12·3%. $C_{14}H_{13}O_3N_2Cl$ requires equiv., 292·5; N, 9·6; Cl, 12·1%).

4-*Chloro*-2-(6-*methoxy*-2-*methyl*-3-*pyridylamino*)*benzoic Acid*.—2 : 4-Dichlorobenzoic acid (25 g.), potassium carbonate (8 g.), 5-amino-2-methoxy-6-methylpyridine (14 g.), amyl alcohol (100 c.c.), copper oxide (0·1 g.), and cuprous iodide (0·1 g.) (5 hr. at 132°) gave an *acid* (17·7 g.) which crystallised from 95% alcohol in yellow prisms, m. p. 228—230° (Found: equiv., 292; N, 9·7; Cl, 12·1%. $C_{14}H_{13}O_3N_2Cl$ requires equiv., 292·5; N, 9·6; Cl, 12·1%).

1 : 10-*Diaza-anthracenes*

6 : 9-*Dichloro*-2-*methoxy*-1 : 10-*diaza-anthracene*.—Anhydrous 4-chloro-2-(6-methoxy-3-pyridylamino)benzoic acid (54 g.) was refluxed with freshly distilled phosphoryl chloride (330 c.c.) for 4 hr. Excess of phosphoryl chloride (*ca.* 250 c.c.) was pumped off (at 70°) and the residual thick liquid poured slowly on crushed ice (1500 g.) and aqueous ammonia (500 c.c.; *d* 0·88). More ice and ammonia were added when necessary to keep the temperature at 0° and the mixture just alkaline. After 6—12 hr. at 0° the friable solid was collected, washed with ice water, and dried (KOH) at 15°/5 mm. The 6 : 9-*dichloro*-2-*methoxy*-1 : 10-*diaza-anthracene* (53 g.) was obtained as a light yellow powder, m. p. 180—184°, pure enough for the next stage; a sample crystallised from acetone in yellow needles, m. p. 186—188° (Found: N, 10·4; Cl, 24·9. $C_{13}H_8ON_2Cl_2$ requires N, 10·0; Cl, 25·4%).

The following compounds were obtained in the same manner from the appropriate 2-3′-pyridylaminobenzoic acid; in all cases the yield of crude material (having m. p. *ca.* 4° below the m. p. of the recrystallised material) was *ca.* 95%. These 9-chloro-1 : 10-diaza-anthracenes are very soluble in chloroform, less soluble in benzene, and still less soluble in ligroin. They are stable in aqueous media provided they are slightly alkaline and may be crystallised from aqueous ammoniacal alcohol; in aqueous media sufficiently acid for the central nitrogen atom to become protonised, the 9-chloro-substituent rapidly undergoes hydrolysis (cf. 5-chloroacridines). The crystallising solvent is given in parentheses.

2-n-*Butoxy*-6 : 9-*dichloro*-1 : 10-*diaza-anthracene*, light yellow needles (acetone), m. p. 126—128° (Found: N, 8·9; Cl, 22·0. $C_{16}H_{14}ON_2Cl_2$ requires N, 8·7; Cl, 22·1%).

6 : 9-*Dichloro*-2-*phenoxy*-1 : 10-*diaza-anthracene*, colourless needles (large volume of ligroin, b. p. 80—100°), m. p. 184° (Found: N, 8·2; Cl, 20·5. $C_{18}H_{10}ON_2Cl_2$ requires N, 8·2; Cl, 20·8%).

9-*Chloro*-2 : 7-*dimethoxy*-1 : 10-*diaza-anthracene* [obtained by cyclisation of 5-methoxy-2-(6-methoxy-3-pyridylamino)benzoic acid], colourless needles (ligroin, b. p. 80—100°), m. p. 220° alone and on admixture with a sample obtained by cyclisation of 6-methoxy-3-*p*-methoxyanilinopicolinic acid (see below) (Found: N, 10·4; Cl, 13·2. $C_{14}H_{11}O_2N_2Cl$ requires N, 10·2; Cl, 12·9%).

6 : 9-*Dichloro*-2-*methoxy*-4-*methyl*-1 : 10-*diaza-anthracene*, pale lemon-yellow needles (ethyl acetate), m. p. 171—173° (Found: N, 9·6; Cl, 24·4. $C_{14}H_{10}ON_2Cl_2$ requires N, 9·55; Cl, 24·2%).

2 : 7 : 9-*Trichloro*-1 : 10-*diaza-anthracene*.—5-Chloro-2-(6-benzyloxy-3-pyridylamino)benzoic acid (12 g.) and phosphoryl chloride (75 c.c.) were refluxed for 4 hr. The crude product, isolated as above, was drained on tile and dried (KOH) at 15°/2 mm. Washing with a little cold ligroin (b. p. 40—60°) gave 2 : 7 : 9-*trichloro*-1 : 10-*diaza-anthracene* as a buff powder (9 g.), m. p. 230—234°; it crystallised from carbon tetrachloride–ligroin (b. p. 80—100°) in pale olive needles, m. p. 238—240° (Found: N, 9·9; Cl, 37·4. $C_{12}H_5N_2Cl_3$ requires N, 9·9; Cl, 37·6%).

2 : 6 : 9-*Trichloro*-1 : 10-*diaza-anthracene* was obtained in the same manner in 80% yield from 4-chloro-2-(6-benzyloxy-3-pyridylamino)benzoic acid as pale yellow needles, m. p. 228—230° (Found: N, 10·2; Cl, 37·9%).

2 : 9-*Dichloro*-1 : 10-*diaza-anthracene*, obtained in 75% yield from 2-(6-benzyloxy-3-pyridylamino)benzoic acid by similar means, crystallised from chloroform–ligroin (b. p. 60—80°) in felted colourless needles, m. p. 200° (Found: N, 11·3; Cl, 28·4. $C_{12}H_6N_2Cl_2$ requires N, 11·2; Cl, 28·5%).

Attempted Cyclisation of 4-*Chloro*-2-(6-*methoxy*-2-*methyl*-3-*pyridylamino*)*benzoic Acid*.—This acid (10 g.) was refluxed for 4 hr. with phosphorus oxychloride (100 c.c.), the excess of oxychloride distilled off at reduced pressure, and the residual oil poured on crushed ice and ammonia. The precipitate was collected, drained, and extracted with chloroform. The extract, on evaporation, gave a dark sticky solid, which was converted in benzene into a grey powder; crystallisation of this from aqueous alcohol containing a little ammonia yielded the *benzamide* (1·5 g.),

m. p. 182—184° (Found: N, 14·9; Cl, 12·4. $C_{14}H_{14}O_2N_3Cl$ requires N, 14·4; Cl, 12·2%). Hydrolysis of this (0·8 g.) with 5N-sodium hydroxide (10 c.c.) in alcohol (10 c.c.) yielded the original acid, m. p. and mixed m. p. 228—230°. No 9-chloro-1 : 10-diaza-anthracene or 1 : 10-diaza-anthrone was isolated.

9-Amino-6-chloro-2-methoxy-1 : 10-diaza-anthracene.—A solution of 6 : 9-dichloro-2-methoxy-1 : 10-diaza-anthracene (8·6 g.) in phenol (40 g.; previously dried at 130° for 1 hr.) was heated to 110° for 1 hr., and then ammonium carbonate (20 g.) was added portionwise as rapidly as the frothing would permit (*ca.* 1 hr.). After a further 1½ hr. at 110° the mixture was cooled and poured into, and macerated with, dry ether (400 c.c.). Next morning the crystalline yellow *hydrochloride* (8·6 g.; m. p. 282—284°) was collected, washed with ether, and dried at 50° (Found: N, 14·0; Cl, 23·8. $C_{13}H_{11}ON_3Cl_2$ requires N, 14·2; Cl, 24·0%). The free *amine* was obtained by shaking a suspension of the hydrochloride in an excess of 2N-sodium hydroxide with glass beads for 3 hr.; the insoluble material crystallised from aqueous pyridine in pale yellow needles, m. p. 294—296° (Found: N, 16·4; Cl, 14·9. $C_{13}H_{10}ON_3Cl$ requires N, 16·2; Cl, 13·7%).

9-Amino-2-n-butoxy-6-chloro-1 : 10-diaza-anthraceme hydrochloride, obtained in the same manner in 90% yield, crystallised from methanol containing a trace of hydrochloric acid in yellow needles, m. p. 254—256° (decomp.) (Found: N, 12·5; Cl, 21·0. $C_{16}H_{17}ON_3Cl_2$ requires N, 12·4; Cl, 21·0%).

9-Amino-6-chloro-2-phenoxy-1 : 10-diaza-anthracene hydrochloride crystallised from ethanol in yellow prisms, m. p. 278—280° (decomp.) (Found: N, 11·7; Cl, 20·2. $C_{18}H_{13}ON_3Cl_2$ requires N, 11·7; Cl, 19·8%).

9-Amino-2-chloro-1 : 10-diaza-anthracene hydrochloride was obtained from 2 : 9-dichloro-1 : 10-diaza-anthracene in like manner. The crude product precipitated by ether was a black powder; this was ground with excess of cold 5N-sodium hydroxide, the insoluble residue dissolved in butanol containing a little ether and the filtered (charcoal) solution extracted with aqueous acetic acid. The solution was basified with sodium hydroxide, and the precipitate dissolved in hot 2N-hydrochloric acid; 9-amino-2-chloro-1 : 10-diaza-anthracene hydrochloride separated in yellow needles (Found: N, 16·1; Cl, 27·4; Cl^-, 13·8. $C_{12}H_8N_3Cl,HCl$ requires N, 15·8; Cl, 26·7; Cl^-, 13·4%). The free base had m. p. 240—244°.

9-Benzylamino-6-chloro-2-methoxy-1 : 10-diaza-anthracene Hydrochloride.—6 : 9-Dichloro-2-methoxy-1 : 10-diaza-anthracene (5 g.) and benzylamine (15 g.) were heated to 120° for 4 hr. and poured into acetone (100 c.c.). The precipitated *hydrochloride* (5·6 g., 81%) crystallised from 95% alcohol as a yellow powder, m. p. 274—276° (Found: N, 10·7; Cl, 18·4. $C_{20}H_{17}ON_3Cl_2$ requires N, 10·9; Cl, 18·4%).

2 : 9-Bis-p-chloroanilino-1 : 10-diaza-anthracene.—2 : 7-Dichloro-1 : 10-diaza-anthracene (5 g.) was refluxed with *p*-chloroaniline (25 g.) for 5 min., then cooled and the excess of *p*-chloroaniline distilled off in steam. The residue, after extraction with cold 60% pyridine, was dissolved in boiling 80% dioxan (200 c.c.), and the solution adjusted to pH 10 with sodium hydoxide and diluted with boiling water (500 c.c.); the *product* (3·3 g.) separated as an orange microcrystalline powder, m. p. 268—270° (Found: N, 13·0; Cl, 16·8. $C_{24}H_{16}N_4Cl_2$ requires N, 13·0; Cl, 16·5%).

6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene Dihydrochloride (" Azacrin ").—A solution of 6 : 9-dichloro-2-methoxy-1 : 10-diaza-anthracene (8·6 g.) in dried phenol (40 g.) was heated to 110° for 1 hr., 2-amino-5-diethylaminopentane (4·8 g., 1·1 mol.) was added dropwise with stirring during ½ hr., and the mixture kept at 110° for a further 1½ hr. The cooled mixture was poured into anhydrous ether (500 c.c.) containing 7·5N-ethanolic hydrogen chloride (4·2 c.c.); the precipitate of reddish-black tar solidified on being set aside with occasional scratching. The resulting orange solid was filtered off, washed with ether, drained, and dissolved in warm water (40 c.c.), and the filtered solution (charcoal) was diluted with acetone (400 c.c.). In the refrigerator the solution deposited 8·6 g. (58%) of a yellow microcrystalline powder, m. p. 172—174° (decomp.) with sintering at 165°. This was the *dihydrochloride trihydrate* (Found: loss of wt. at 100°; 11·2%. Required for trihydrate: 10·2%). Dehydration at 100°/2 mm. yielded the anhydrous *dihydrochloride* as a yellow powder, m. p. 224—226° (Found: N, 12·0; Cl, 22·2. $C_{22}H_{31}ON_4Cl_3$ requires N, 11·8; Cl, 22·5%). The compound is slightly hygroscopic.

The following compounds were prepared by heating the 9-chloro-compound (0·02 mol.) in phenol (40 g.) with the dialkylaminoalkylamine (0·022 mol.) in the same manner and pouring the mixture into anhydrous ether or acetone; it was necessary, however, to isolate and purify the salts by differing means. The yields are given in parentheses.

6-*Chloro*-2-*methoxy*-9-2′-*morpholinoethylamino*-1 : 10-*diaza*-*anthracene dihydrochloride*. The crude compound was dissolved in boiling water (200 c.c.), hot 2N-hydrochloric acid (*ca.* 50 c.c.) added until crystallisation commenced, and the solution set aside; the compound separated in yellow needles (81%), m. p. 258—260° (Found: N, 12·6; Cl, 23·9. $C_{19}H_{23}O_2N_4Cl_3$ requires N, 12·6; Cl, 23·9%).

6-*Chloro*-2-*methoxy*-9-2′-*piperidinoethylamino*-1 : 10-*diaza*-*anthracene dihydrochloride* was obtained in the same manner in yellow needles (68%), m. p. 248—250° (Found: N, 12·9; Cl, 23·8. $C_{20}H_{25}ON_4Cl_3$ requires N, 12·6; Cl, 24·0%).

2-n-*Butoxy*-6-*chloro*-9-2′-*diethylaminoethylamino*-1 : 10-*diaza*-*anthracene dihydrochloride*. Crystallisation of the crude product from ethanol containing a trace of 2N-hydrochloric acid gave the pure salt in light yellow needles, m. p. 228—230° (decomp.) (Found: N, 11·9; Cl, 22·4. $C_{22}H_{31}ON_4Cl_3$ requires N, 11·8; Cl, 22·5%).

2-n-*Butoxy*-6-*chloro*-9-(4-*diethylamino*-1-*methylbutylamino*)-1 : 10-*diaza*-*anthracene dihydrochloride*. The crude product was ground with dry acetone to remove dark colouring matter, and the yellow residue dried at 15°/2 mm. and dissolved in anhydrous ethanol (*ca.* 20 c.c.); the filtered (charcoal) solution was diluted with dry acetone, crystallisation being initiated by scratching. The *dihydrochloride* separated in bright yellow needles, m. p. 174—178° (sintering at 165°) (Found: N, 10·4; Cl, 21·4. $C_{25}H_{37}ON_4Cl_3$ requires N, 10·9; Cl, 20·7%). The *bis*-p-*nitrobenzoate* of the base separated from dilute alcohol in small yellow prisms, m. p. 154—156° (Found: N, 10·9. $C_{39}H_{45}O_9N_6Cl$ requires N, 10·8%).

5-*Acetamido*-2-*methoxy*-6-*methylpyridine*.—5-Amino-2-methoxy-6-methylpyridine (20 g.), mixed with acetic anhydride (16 c.c.), gave, exothermally, the *acetamide* (26 g.), m. p. 130—131° (from ligroin, b. p. 60—80°) (Found: N, 15·9. $C_9H_{12}O_2N_2$ requires N, 15·6%).

3-*Acetamido*-6-*methoxypicolinic Acid*.—A solution of the foregoing crude compound (26 g.) in water (4 l.) was stirred on the water-bath with light magnesium oxide (10 g.) and magnesium sulphate (80 g.); finely powdered potassium permanagnate (80 g.) was added portionwise during ¾ hr. and stirring continued for a further ¼ hr. The mixture was filtered hot and the filter-cake washed with boiling water (1 l.); the combined filtrates were evaporated at reduced pressure to a volume of 1 l., and then extracted with ether (3 × 100 c.c.). The extract on evaporation yielded 1·0 g. of unoxidised starting material; the aqueous solution was acidified with 2N-hydrochloric acid, and the 3-*acetamido*-6-*methoxypicolinic acid* (12 g.; m. p. 186—188°) collected. A sample crystallised from alcohol in colourless needles of the same m. p. (Found: equiv., 210; N, 13·4%. $C_9H_{10}O_4N_2$ requires equiv., 210; N, 13·3%).

3-*Chloro*-6-*methoxypicolinic Acid*.—The foregoing acetamido-acid (6·0 g.) was boiled for ½ hr. with 2·5N-sodium hydroxide (48 c.c.). After addition of 10N-hydrochloric acid (50 c.c.), the solution was diazotised at 0° with sodium nitrite (*ca.* 2·5 g.) in water (15 c.c.), then added dropwise to a stirred solution of cuprous chloride (freshly prepared from 7 g. of hydrated cupric chloride, copper powder, and hydrochloric acid and precipitated with water) in 10N-hydrochloric acid (50 c.c.) at 0—5°; the mixture was stirred for 2 hr. at this temperature and then at 30° for a few minutes until no further nitrogen was evolved. The mixture was diluted with water (165 c.c.) to effect solution and extracted with ether (7 × 50 c.c.), which gave 3-*chloro*-6-*methoxypicolinic acid* (5·0 g.; m. p. 98—100°), forming colourless needles, m. p. 103—104°, from water after removal of copper (Found: equiv., 189; N, 7·5; Cl, 19·1%. $C_7H_6O_3NCl$ requires equiv., 187·5; N, 7·5; Cl, 18·9%).

6-*Methoxy*-3-p-*methoxyanilinopicolinic Acid*.—The foregoing acid (3·75 g., 0·02 mole), potassium carbonate (1·4 g., 0·01 mole), *p*-anisidine (2·5 g.; 0·02 mole), and amyl alcohol (20 c.c.) were stirred at the b. p. for 2 hr. with a trace of copper and copper oxide. Treatment in the manner previously described gave the desired *acid* which crystallised from ligroin (b. p. 80—100°) in yellow needles (1·0 g.), m. p. 108—109° (Found: equiv., 278; N, 10·3%. $C_{14}H_{14}O_4N_2$ requires equiv., 274; N, 10·2%).

9-*Chloro*-2 : 7-*dimethoxy*-1 : 10-*diaza*-*anthracene*.—The anilino-acid (1·6 g.) was refluxed with phosphorus oxychloride (10 c.c.) for 4 hr. and the mixture poured on crushed ice and ammonia. Next morning the precipitate (1·6 g.; m. p. 218°) was collected and dried at 30°; recrystallisation from acetone (250 c.c./g.), with activated alumina as decolorising agent, gave the pure product as a microcrystalline light yellow powder, m. p. 222—223° (Found: N, 10·1; Cl, 12·8. $C_{14}H_{11}O_2N_2Cl$ requires N, 10·2; Cl, 12·9%).

WARD, BLENKINSOP & CO., LTD., RESEARCH DEPARTMENT,
SHEPTON MALLET, SOMERSET.

[*Received, March 4th*, 1954.]

Stages in Oxidations of Organic Compounds by Potassium Permanganate. Part IV. Oxidation of Malonic Acid and its Analogues.*

By Alan Y. Drummond and William A. Waters.

[Reprint Order No. 5044.]

The oxidation of malonic acid by manganic pyrophosphate under nitrogen is completed at the stage $CH_2(CO_2H)_2 + 3O = 2CO_2 + H{\cdot}CO_2H$, tartronic acid being an intermediate. An initial complex, probably $[Mn^{III},CH_2(CO_2H)_2,(H_2P_2O_7)_2]^-$, is first formed and this decomposes by a rate-determining reversible reaction to manganous pyrophosphate and an active radical, $\cdot CH(CO_2H)_2$, capable both of inducing vinyl polymerisation and of oxidising alcohols, ethers, and Mn^{2+} ions. In the presence of oxygen the complete oxidation $CH_2(CO_2H)_2 + 4O = 3CO_2 + 2H_2O$ occurs with consumption of one molecule of oxygen gas per molecule of malonic acid. Oxygen is absorbed by the radical $\cdot CH(CO_2H)_2$, carbon dioxide evolution then sets in, and the molecule $HO{\cdot}O{\cdot}CH(CO_2H)_2$ does not seem to be formed. Oxalic acid seems to be an intermediate in this complete oxidation: mesoxalic acid, if formed, would immediately be oxidised to oxalic acid under these conditions.

Both ethyl- and benzyl-malonic acid give radicals $\cdot CR(CO_2H)_2$ which are incapable of oxidising alcohols or Mn^{2+}, but these acids do form hydroperoxides, $HO{\cdot}O{\cdot}CR(CO_2H)_2$, of low stability. Weakly acid permanganate does not at once oxidise malonic acid. A trace of Mn^{III} must be present to initiate reaction in which the stage $\cdot CH(CO_2H)_2 + (MnO_4)^- \longrightarrow {}^+CH(CO_2H)_2 + (MnO_4)^{2-}$ is important.

The investigation has disclosed a novel example of a radical-induced oxidation, since Mn^{III} does not attack monohydric alcohols in the absence of malonic acid. Oxidising and reducing powers of radicals are discussed in relation to chemical structure.

The mechanism of the oxidation of malonic acid by aqueous potassium permanganate has not yet been studied in detail, though several workers have examined the organic products of the oxidation. Whilst Perdrix (*Bull. Soc. chim.*, 1900, **23**, 645), Cameron and McEwan (*Proc.*, 1910, **26**, 144), and Cartledge and Nichols (*J. Amer. Chem. Soc.*, 1940, **62**, 3057) agree that the oxidation in acid solution is

$$CH_2(CO_2H)_2 + 3O = 2CO_2 + H{\cdot}CO_2H + H_2O$$

Hatcher and West (*Trans. Roy. Soc. Canada*, 1927, **21**, iii, 269) have argued from kinetic observations of the relative rates of oxidation of formic and malonic acid that the reaction is

$$CH_2(CO_2H)_2 + 2O = CO_2 + 2H{\cdot}CO_2H$$

although it is difficult to reconcile this statement with their view that the oxidation proceeds by the stages Malonic acid $\longrightarrow$ Tartronic acid $\longrightarrow$ Glyoxylic acid $\longrightarrow$ CO_2 + Formic acid. This sequence was inferred from the observation that whereas glyoxylic acid is rapidly oxidised by acid permanganate to formic acid and carbon dioxide, mesoxalic acid is completely oxidised to carbon dioxide under similar conditions (Hatcher and Holden, *ibid.*, 1925, **19**, iii, 13; Hatcher, *ibid.*, 1926, **20**, iii, 327). The same sequence also seems to hold for oxidation of malonic acid by hydrogen peroxide (Hatcher and Mueller, *Canad. J. Res.*, 1930, **3**, 291), for its anodic oxidation (Takayama and Miduno, *J. Chem. Soc. Japan*, 1935, **56**, 1460), and for oxidation by periodic acid (Fleury and Courtois, *Compt. rend.*, 1946, **223**, 633; Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621). Alkaline permanganate however oxidises malonic acid to carbon dioxide and oxalic acid:

$$CH_2(CO_2H)_2 + 3O = CO_2 + H_2C_2O_4 + H_2O$$

(Drummond and Waters, Part I, *loc. cit.*).

* Parts I, II, and III, *J.*, 1953, 435, 440, 3119.

Except for the paper last cited, preceding publications give no indication of the way in which the successive valency changes of the manganese determine the detailed mechanism of the oxidation. The present work attempts to deal with this problem by the selective methods that were broadly reviewed in Part I of this series (*loc. cit.*). Since it was found that manganic salts immediately attack malonic acid, whereas cold acid permanganate reacts with it only after an induction period, the oxidation of malonic acid, and subsequently of ethyl- and benzyl-malonic acid, by manganic pyrophosphate was examined in detail, and thereafter the significance of the manganic ion in initiating reactions involving the permanganate anion was demonstrated. Each aspect of the investigation is reviewed in detail in the following sections.

Oxidation of Malonic Acid with Manganic Pyrophosphate.—The manganic pyrophosphate reagent described in Parts II and III oxidises malonic acid at 25—30° at a rate convenient for kinetic study. In all early experiments, carried out in stoppered vessels, it was found that the initial, fairly rapid reaction slowed down considerably after a few minutes and thereafter proceeded steadily for a long time (Fig. 1, curve *A*). All components of the original reaction mixture, including distilled water, brought about a further brief acceleration of the rate of oxidation when added separately to the slowly oxidising system and it was then realised that dissolved oxygen was accelerating the oxidation. Further

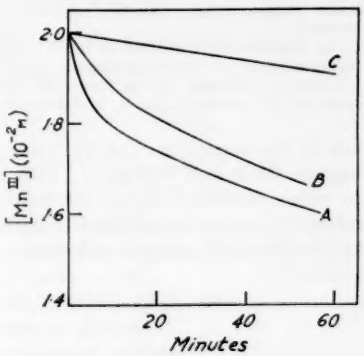


FIG. 1. *Oxidations of malonic acid by manganic pyrophosphate.* pH 1·32; temp. 30·0°.
Initial concns.: Mn^{III} $2{\cdot}00 \times 10^{-2}$M; *malonic acid*, $9{\cdot}26 \times 10^{-2}$M; *pyrophosphate* 0·169M.
A, Reaction in closed vessel.
B, Reaction under nitrogen.
C, Reaction under nitrogen; $4{\cdot}00 \times 10^{-3}$M-*manganous sulphate added.*

experiments revealed that the oxidations of malonic acid (A, see below) in the absence of oxygen and (B) in aerated solutions proceed by quite different reaction mechanisms.

(A) *Reactions in the absence of oxygen.* These were carried out at 30° in stirred solutions through which purified nitrogen was continually bubbled. The rate of reduction of Mn^{III} was easily followed by iodometric titration. Under these conditions the rate of reaction had still decreased considerably when only 10—20% of the manganic salt had been reduced (see Fig. 1, curve *B*). This was due to the retarding effect of manganous ions, for the initial rate of reduction of manganic salt could be decreased and made linear by adding manganous sulphate equivalent to 25% of the initial Mn^{III} (Fig. 1, curve *C*). With such mixtures it was possible to determine initial reaction orders with respect to the various components of the system. Other bivalent cations, such as magnesium and zinc which also form complexes with pyrophosphate, had no corresponding action.

Possible explanations of the retarding action of manganous ions are (*a*) that the active oxidising agent is in this case Mn^{4+}, produced by the rapid reversible disproportionation

$$2Mn^{3+} \rightleftharpoons Mn^{2+} + Mn^{4+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and (*b*) that the initial stage of the oxidation effected by the manganic ion is reversible

$$Mn^{3+} + CH_2(CO_2H)_2 \rightleftharpoons Mn^{2+} + H^+ + \cdot CH(CO_2H)_2 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Hypothesis (*a*) is most improbable since it has been shown that an excess of pyrophosphate so strongly displaces the equilibrium (1) in favour of tervalent manganese complexes that there is no evidence of the existence of any quadrivalent manganese complexes in aqueous solutions of moderate acidity (Kolthoff and Watters, *Ind. Eng. Chem. Anal.*, **1943**, **15**, 8;

Lingane and Karplus, *ibid.*, 1946, **18**, 191; Watters and Kolthoff, *J. Amer. Chem. Soc.*, 1948, **70**, 2455). Again, manganic pyrophosphate does not attack compounds such as ethanol and *iso*propanol which are thought to be oxidised by Mn^{4+} (Merz, Stafford, and Waters, *J.*, 1951, 638). Moreover equation (1) cannot be reconciled with the observed reaction orders.

The reversibility of reaction (2) is however in full accord with experimental facts, since (i) the oxidation rate is considerably accelerated by adding vinyl cyanide, which removes the initial radical $\cdot CH(CO_2H)_2$ as an insoluble polymer containing carboxyl groups (Drummond and Waters, *J.*, 1953, 2836), and (ii) the oxidising mixture has been proved to contain a new potent oxidising agent capable of attacking monohydric alcohols and ethers which are unaffected by manganic pyrophosphate. These coupled oxidations immediately increase the rate of reduction of Mn^{III} and must therefore be related to the first stage of the oxidation of the malonic acid, and not to the oxidation of later reaction products such as tartronic acid. Table 1 lists, in increasing order of their accelerating effects, the substances which have been tested. It is significant that the oxidisable com-

TABLE 1. *Organic compounds affecting the rate of reaction of malonic acid with manganic pyrophosphate under nitrogen.*

Substances without effect: Acetic, succinic, and adipic acid; ethyl acetate; chloral hydrate; *tert.*-butanol.

Substances accelerating reduction of Mn^{III}: Methanol (gives formaldehyde) < dioxan < formic acid < formaldehyde < tetrahydropyran < diethyl ether (gives acetaldehyde) < vinyl cyanide (gives polymer) < ethanol (gives acetaldehyde) < propanol (gives propaldehyde) < *iso*propanol (gives acetone) ≪ crotonic acid < maleic and fumaric acid.

pounds in the second section of Table 1 are oxidised by Fenton's reagent by the chain mechanism (Merz and Waters, *J.*, 1949, S 15) and therefore yield strongly reducing radicals of low redox potential, $E_{(-e)}$ (Mackinnon and Waters, *J.*, 1953, 323). The induced oxidations can therefore be ascribed to hydrogen-atom transfers, such as (3), followed by fast oxidations (4) which compete effectively with the much slower oxidation (5) of the malonic acid radical:

$$HO\cdot CH_2{-}H + \cdot CH(CO_2H)_2 \longrightarrow HO\cdot CH_2\cdot + H\cdot CH(CO_2H)_2 \quad (3)$$

$$HO\cdot CH_2\cdot + Mn^{3+} \longrightarrow CH_2O + H^+ + Mn^{2+} \quad (4)$$

$$Mn^{3+} + \cdot CH(CO_2H)_2 \longrightarrow Mn^{2+} + H^+ + {}^+CH(CO_2H)_2 \quad (5)$$

$$H_2O + {}^+CH(CO_2H)_2 \longrightarrow HO\cdot CH(CO_2H)_2 + H^+ \ (Immediate) \quad (6)$$

Theoretical implications of these radical-coupled oxidations are examined below (p. 2466).

In prolonged oxidations of malonic acid by manganic pyrophosphate it was found that carbon dioxide was evolved and that formic acid remained in solution after complete reaction. When excess of manganic salt was present a total of 5·95 equivalents of Mn^{III} were eventually destroyed per molecule of malonic acid in the complete absence of oxygen. Consequently the equation $CH_2(CO_2H)_2 + 3O = 2CO_2 + H\cdot CO_2H + H_2O$ adequately represents the stoicheiometry of the oxidations of malonic acid by both cold acid permanganate and manganic cations. Tartronic, mesoxalic, glycollic, glyoxylic, and oxalic acids are all possible intermediates. Of these, mesoxalic and oxalic acids can at once be excluded since manganic pyrophosphate oxidises them completely to carbon dioxide. Glycollic acid too can be excluded since it is oxidised much more slowly than is the malonic acids: had it been formed the oxidation rate would have decreased noticeably when only two equivalents of Mn^{III} had been consumed, and this is not the case. Both tartronic and glyoxylic acids are oxidised rapidly by manganic pyrophosphate and both yield formic acid as well as carbon dioxide. Consequently the complete course of the oxidation by Mn^{III} can be written:

$$CH_2(CO_2H)_2 \longrightarrow HO\cdot CH(CO_2H)_2 \longrightarrow CO_2 + OCH\cdot CO_2H \longrightarrow CO_2 + H\cdot CO_2H$$

Two equivalents of Mn^{III} are needed in each of these three stages and presumably therefore each of them involves the transient formation of an organic free radical.

The initial rates of oxidation indicate a reaction order with respect to malonic acid of

rather less than one, and this, together with the fact that, at constant pH, the rate of oxidation decreases when the pyrophosphate concentration is increased, indicates that the rate-determining oxidation stage is preceded by the rapid reversible formation of a chelated manganic complex, similar to that which is involved in the oxidation of pinacol (Part III). Malonate complexes of tervalent manganese have been described by Cartledge and Nichols (*loc. cit.*), Taube (*Chem. Reviews*, 1952, **50**, 69; *J. Amer. Chem. Soc.*, 1948, **70**, 3926), and Meyer and Schramm (*Z. anorg. Chem.*, 1921, **123**, 56). These workers have shown that the chelate association is labile and that the complexes soon decompose in acidified solutions.

By neglecting the possible formation of pyrophosphate–dimalonato-complexes when pyrophosphate is present in large excess and also the formation of complexes in which tartronic acid has displaced malonic acid, and further by assuming that the malonate radical $\cdot CH(CO_2H)_2$ reacts with any Mn^{III} ion without prior complex formation, the kinetics of the initial stages of the oxidation can be evaluated from the reaction sequences (7, 8, 5, 6, 9, 10) in which one typical pyrophosphate ion has been selected as representative of those concerned in oxidations throughout the whole of the possible pH range.

$$CH_2(CO_2H)_2 + [Mn(H_2P_2O_7)_3]^{3-} \overset{K_1}{\rightleftharpoons} (H_2P_2O_7)^{2-} + [Mn,CH_2(CO_2H)_2,(H_2P_2O_7)_2]^- \text{ (Instantaneous)} \quad . \quad (7)$$

$$[Mn,CH_2(CO_2H)_2,(H_2P_2O_7)_2]^- \underset{k_3}{\overset{k_2}{\rightleftharpoons}} \cdot CH(CO_2H)_2 + H^+ + [Mn(H_2P_2O_7)_2]^{2-} \quad . \quad . \quad (8)$$

(*Both measurably slow*)

$$Mn^{III} + \cdot CH(CO_2H)_2 + H_2O \xrightarrow{k_4} Mn^{II} + H^+ + HO\cdot CH(CO_2H)_2 \quad . \quad . \quad . \quad . \quad (5, 6)$$

$$HO\cdot CH(CO_2H)_2 + Mn^{III} \xrightarrow{k_5} \cdot CH(OH)\cdot CO_2H + CO_2 + H^+ + Mn^{II} \quad . \quad . \quad (9)$$

$$\cdot CH(OH)\cdot CO_2H + Mn^{III} \longrightarrow O\cdot CH\cdot CO_2H + H^+ + Mn^{II} \text{ (Fast)} \quad . \quad . \quad . \quad (10)$$

The oxidation of the tartronic acid will undoubtedly involve formation and breakdown of a chelated complex, but since it is faster than the oxidation of malonic acid the simplified equation (9) adequately represents its significant oxidation stage.

From this scheme, by assuming that the radical $\cdot CH(CO_2H)_2$ attains a stationary concentration, it can be deduced that the initial rate

$$-d[Mn^{III}]/dt = 2K_1 \cdot k_2k_4 \cdot \frac{[CH_2(CO_2H)_2]}{[(H_2P_2O_7)^{2-}] + K_1[CH_2(CO_2H)_2]} \cdot \frac{[Mn^{III}]^2 + k_5[Mn^{III}]^3 \cdot t}{k_3[Mn^{II}] + k_4[Mn^{III}]}$$

where the term $k_5[Mn^{III}]^3 \cdot t$ represents the small additional oxidation of the tartronic acid present at time t after the start of the reaction, and is a first-order approximation that is valid provided that the concentration of the tartronic acid in the system is low.

Fig. 2 shows that the initial value of $-d[Mn^{III}]/dt$ varies as a[Malonic acid]/(b + [Malonic acid]) when the concentration of *free* malonic acid [$CH_2(CO_2H)_2$] has been computed from the initial total concentration of malonic acid by the approximation method described in Part III. Figs. 3 and 4 show that the expected reaction orders with respect to both [Mn^{III}] and [Mn^{II}] hold, provided that $k_3 \gg k_4$, which is necessarily the case since a small amount of manganous salt has a very noticeable effect on the reaction velocity (compare Fig. 1, curves *B* and *C*). It may be noted that since $k_3 \gg k_4$ the reaction order with respect to [Mn^{III}] never falls below *two*, and that it rises beyond this only under the conditions in which the term $k_5[Mn^{III}]^3 \cdot t$ becomes of significance, *i.e.*, at high concentrations of manganic salts.

If glycollic acid, and not tartronic acid, had been an intermediate product, through the occurrence of reaction (11), then at high concentrations of Mn^{III} the reaction order with

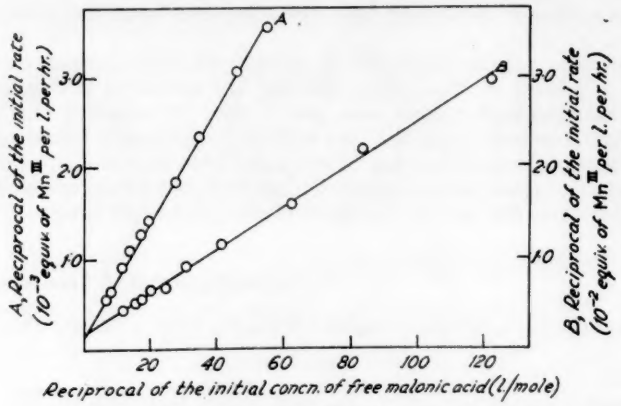
$$\cdot CH(CO_2H)_2 + Mn^{III} + H_2O \longrightarrow HO\cdot CH_2\cdot CO_2H + H^+ + CO_2 + Mn^{II} \quad . \quad . \quad (11)$$

respect to [Mn^{III}] should fall below two instead of rising above it, because the rate of oxidation of glycollic acid is negligible.

(B) *Reactions in the presence of oxygen.* Oxygen accelerates the rate of oxidation of malonic acid by manganic pyrophosphate so much that comparative reaction velocities

could be obtained only by lowering the temperature to 25° and decreasing the acidity to the pH range 2·0—2·6. Since many organic free radicals combine with oxygen to give radicals which then form hydroperoxides, RO_2H, of moderate stability, or sometimes hydrogen peroxide, both of which would invalidate iodometric titration of Mn^{III}, colorimetric measurements were made which showed that, within their accuracy, oxidising

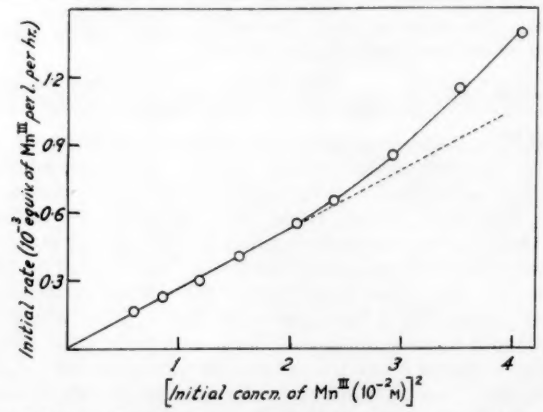
FIG. 2. *Reaction orders with respect to malonic acid.*



A, Reaction in nitrogen: pH 0·92; temp. 30·0°.
Initial concns.: Mn^{III} $1·67 \times 10^{-2}$M; *manganous sulphate*, $4·18 \times 10^{-3}$M; *pyrophosphate*, 0·146M.

B, Reaction in oxygen: pH 2·05; temp. 25·0°.
Initial concns.: Mn^{III} $2·07 \times 10^{-2}$M; *pyrophosphate*, 0·178M.

FIG. 3. *Oxidation of malonic acid under nitrogen; reaction order with respect to* [Mn^{III}].



pH 0·80; *temp.* 30·0°. *Initial concns.*: *malonic acid*, $7·31 \times 10^{-2}$M; Mn^{II}, $5·83 \times 10^{-3}$M; *pyrophosphate* 0·134M.

solutions contain negligible concentrations of hydroperoxides. Tests with titanic sulphate confirmed the absence of hydrogen peroxide after complete reaction.

Solutions of malonic acid which have been completely oxidised by the combined action of manganic pyrophosphate and oxygen do not give positive chromotropic acid tests for the presence of formic acid (Feigl, " Spot Tests," Elsevier Publ. Co., Amsterdam, 1947), so that evidently the oxygen must alter the whole reaction sequence, preventing the formation of tartronic or glyoxylic acid and assisting complete oxidation to carbon dioxide

and water. The oxygen undoubtedly acts at an early stage in the oxidation sequence because its absorption sets in immediately at its maximum rate. Moreover, the rates of the ærobic oxidations, unlike those of anærobic oxidations, are not altered by the addition of manganous cations, but can be reduced slightly by adding high concentrations of methanol or ethanol. Carbon dioxide is evolved from the commencement of the oxidation and consequently it was necessary to use Warburg micro-respirometers containing caustic alkali for measurement of oxygen uptake.

Table 2, in which the oxygen uptake of a reacting mixture is compared with the extent of reduction of Mn^{III}, shows that the two reactions proceed at related speeds; this would be the case if the simplified reaction (2) (p. 2457) was immediately followed by (12) to the complete exclusion of reactions (5), (6), (9), and (10) of the anaerobic oxidation sequence, for the ratio R = (Moles of O_2 absorbed)/(Equivs. of Mn^{III} reduced) remains constant though the oxidation rate decreases as the manganic salt is consumed.

$$O_2 + \cdot CH(CO_2H)_2 \longrightarrow \cdot O \cdot O \cdot CH(CO_2H)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Table 3 gives final values for this ratio R after complete reduction of Mn^{III} for different mixtures all initially containing malonic acid in excess. The bigger the initial excess of malonic acid the more will the measurements relate to the early stages (2) and (12) of the ærobic oxidation: as expected this condition favours high values of R. R also increases when the rate of oxidation is diminished by increasing the pH of the solution.

TABLE 2. *Oxidation of malonic acid by the combined action of manganic pyrophosphate and oxygen.* Temp. 35·08°; pH 2·35.

Initial concns. (M): Mn^{III} $1·63 \times 10^{-2}$; malonic acid $2·19 \times 10^{-2}$; pyrophosphate $1·41 \times 10^{-1}$.

Time (min.)	Oxygen absorbed (10^{-3} mole/l.)	Mn^{III} reduced (10^{-3} equiv./l.)	Ratio, R	Time (min.)	Oxygen absorbed (10^{-3} mole/l.)	Mn^{III} reduced (10^{-3} equiv./l.)	Ratio, R
2	0·19	0·65	0·285	40	2·99	11·1	0·269
4	0·43	1·40	0·307	50	3·35	12·4	0·270
6	0·56	2·12	0·264	60	3·61	13·4	0·269
10	0·97	3·59	0·270	70	3·79	14·1	0·269
14	1·37	5·00	0·275	80	3·91	14·6	0·268
20	1·84	6·82	0·270	90	4·03	15·0	0·269
28	2·36	8·79	0·268	∞	4·47	16·3	0·274

TABLE 3. *Completed oxidations of malonic acid by* Mn^{III} *in the presence of oxygen.* Temp. 35·08°.

Initial concentrations				Ratio, R	
Mn^{III} (10^{-2}M)	Pyrophosphate (M)	Malonic acid (M)	pH	Final value	Standard deviation (%)
1·20	0·154	0·795	1·15	0·424	1·0
1·20	0·154	0·144	2·41	0·366	1·5
1·20	0·154	0·144	1·15	0·308	0·7
1·79	0·154	0·144	1·15	0·280	0·2
1·20	0·103	0·072	0·96	0·281	0·5
1·20	0·154	0·024	1·15	0·283	0·5

A lower limit of $R = 0·25$ should be reached if complete oxidation of each mole of malonic acid to carbon dioxide and water were attained by the consumption of one mole of oxygen and four equivs. of Mn^{III}:

$$CH_2(CO_2H)_2 + O_2 + 4Mn^{3+} = 3CO_2 + 4H^+ + 4Mn^{2+}$$

It was difficult however to ensure complete oxidation of malonic acid even by excess of oxygen-saturated solutions of manganic pyrophosphate, for after 12—48 hr. the insoluble red manganic hydrogen phosphate described in Part I is deposited and reaction ceases though only 3·5—3·8 equivalents of Mn^{III} have then been consumed per mole of malonic acid. Since formic acid could not be detected in the resulting solutions it is unlikely that the anærobic sequence had comprised 10—25% of the whole reaction. A more probable explanation is that at low manganic concentrations one of the later stages of the ærobic

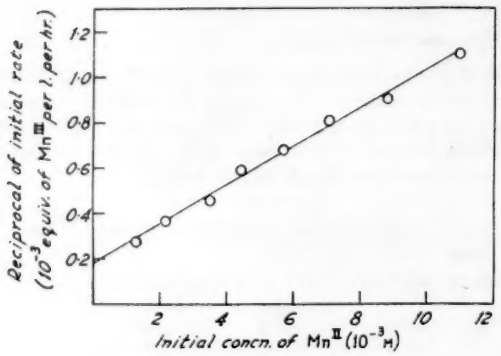
oxidation sequence becomes so slow that oxidation to carbon dioxide is not complete. We tentatively suggest that a little oxalic acid may remain, for, as Fig. 5 shows, the reaction

$$H_2C_2O_4 + 2Mn^{3+} = 2CO_2 + 2H^+ + 2Mn^{2+}$$

is slow at pH 2·54 in the presence of pyrophosphate, and would cease almost completely when deposition of manganic hydrogen phosphate leaves only a very minute concentration of Mn^{III} in solution. Fig. 5 also shows that the oxidation of mesoxalic acid to oxalic acid is almost instantaneous under similar conditions.

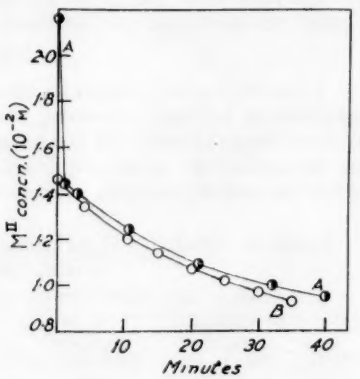
To account for the stages of the ærobic reactions of malonic acid which may follow the

FIG. 4. *Oxidation of malonic acid under nitrogen; reaction order with respect to* Mn^{II}.



pH 0·79; *temp.* 30·0°. *Initial concns.*: Mn^{III}, 1·76 × 10^{-3}M; *malonic acid*, 8·52 × 10^{-2}M; *pyrophosphate*, 0·153M.

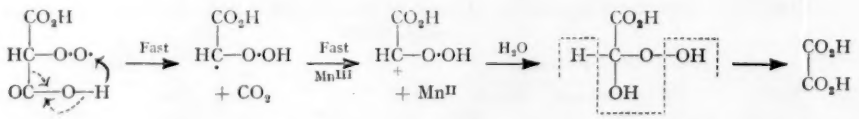
FIG. 5. *Oxidations of mesoxalic and oxalic acids.*



A, *Mesoxalic acid*, 3·52 × 10^{-3}M, *at* pH 2·51. *B*, *Oxalic acid*, 3·52 × 10^{-3}M, *at* pH 2·54. *Temp.* 30·0°. *Pyrophosphate*, 0·179M.

production of the peroxy-radical by reaction (12) the following three mechanisms are rational:

(i)



(ii)

$$(HO_2C)_2CH{\cdot}O_2{\cdot} + CH_2(CO_2H)_2 \longrightarrow (HO_2C)_2CH{\cdot}O{\cdot}OH + {\cdot}CH(CO_2H)_2 \quad . \; . \quad (13)$$

$$(HO_2C)_2CH{\cdot}O_2H \xrightarrow{\text{Fast}} (HO_2C)_2CO$$
$$(HO_2C)_2CO + 2Mn^{3+} \xrightarrow{\text{Fast}} CO_2 + H_2C_2O_4 \quad \} \quad . \; . \; . \; . \; . \; . \; . \; . \quad (14)$$

(iii)

$$(HO_2C)_2CH{\cdot}O{\cdot}O{\cdot} + Mn^{2+} + H^+ \xrightarrow{\text{Fast}} (HO_2C)_2CH{\cdot}O{\cdot}OH + Mn^{3+} \quad . \; . \; . \; . \quad (15)$$

immediately followed by (14).

Scheme (i), not involving the formation of a hydroperoxide molecule, postulates an intramolecular hydrogen switch and immediate loss of carbon dioxide to give a carbon radical which by further oxidation by one equivalent of Mn^{III} would give oxalic acid. The rate of oxidation then depends essentially on the rate of formation of the initial radical, ·$CH(CO_2H)_2$.

Scheme (ii) requires that the unknown hydroperoxide of malonic acid, formed by the usual metallic ion-catalysed autoxidation chain [reactions (12) and (13) consecutively], breaks down at once to mesoxalic acid which, as has been shown, is immediately oxidised to oxalic acid.

Scheme (iii), an alternative chain sequence for manganic salt-catalysed autoxidation of malonic acid to mesoxalic acid, is the least likely since Mn^{2+} has been shown to have no effect on the reaction rate, but it cannot be quite excluded since the ensuing rapid oxidation of mesoxalic acid to oxalic acid might mask any observable effect of change of Mn^{2+} concentration. This postulate would require reaction (15) to be so fast that it would not be rate-significant provided that a trace of Mn^{2+} was present in the solution. Reaction (15) however does seem to be important in the ærobic oxidations of both ethyl- and benzyl-malonic acids (see p. 2465).

The chain oxidation (ii) also does not appear to be of great significance because, as Table 2 clearly shows, the rate of oxygen uptake is, from the first, strictly proportional to the rate of Mn^{III} reduction and the ratio R does not fall from the high value of 0·5 as would be the case if the initial catalytic formation of the radical $\cdot CH(CO_2H)_2$ (reaction 2) initiated the chain of reactions (12) and (13), giving the hydroperoxide molecule which then consumed two equivalents of Mn^{III} (reaction 14). Again, long reaction chains do not occur because the rate of consumption of oxygen, or of Mn^{III}, does not accord with the theoretical kinetics for such processes {the possibilities are $-d[O_2]/dt$ = approx. $-$ $2d[Mn^{III}]/dt$ varying as $[Mn^{III}][CH_2(CO_2H)^2/[Mn^{II}]$ for chain ending by reaction (15), or as $[O_2][CH_2(CO_2H)_2]$ for chain ending by reaction (5) of the anærobic sequence}, but the rate is undoubtedly governed by the forward reactions (7) and (8) between malonic acid and manganic pyrophosphate which require the initial reversible formation of a chelated manganic complex. As in the anærobic oxidation 1/(Initial rate) varies as a[Malonic acid]/(b + [Malonic acid]) (see Fig. 2). The initial reaction order with respect to Mn^{III} is 1·10 and not exactly unity (see Table 4). This can be expected when the secondary oxidations are faster than the initial step [reactions (7) and (8)].

Scheme (i), not requiring the formation of a hydroperoxide molecule, $HO_2 \cdot CH(CO_2H)_2$, provides, on balance, the most plausible explanation of the available experimental facts, but if very short reaction chains only are involved then scheme (ii) or (iii) may still be cogent. Undoubtedly the uptake of oxygen by the radical $\cdot CH(CO_2H)_2$ [reaction (12)] must be much more rapid than the oxidation of manganous ions by this radical and further reactions of the radical $\cdot O \cdot O \cdot CH(CO_2H)_2$ must be intimately coupled with reactions which consume more Mn^{III}.

The slight retarding actions of methanol and ethanol can easily be accounted for by concluding that the hydrogen-transfer reactions (3) (p. 2458) occur at rates approaching that of (12) and give radicals, $\cdot CH_2 \cdot OH$, etc., which are less reactive to oxygen than is $\cdot CH(CO_2H)_2$.

TABLE 4. *Oxidation of malonic acid in oxygen : reaction order with respect to* Mn^{III}.

A. pH 2·40; temp. 25·0°. Initial [Malonic acid] = 0·0367M. [Pyrophosphate] = 0·189M.

Initial rate (10^{-3} equiv. of Mn^{III} per l. per hr.)	$[Mn^{III}]$ (10^{-3}M)	Rate/$[Mn^{III}]^{1\cdot10}$
3·82	6·7	941
4·65	8·1	930
6·10	10·8	893
8·06	13·5	918
9·90	16·2	917
10·7	17·5	915

B. pH 2·47; temp. 25·0°. Initial [Malonic acid] 0·0347M. [Pyrophosphate] 0·238M.

Initial rate (10^{-3} equiv. of Mn^{III} per l. per hr.)	$[Mn^{III}]$ (10^{-3})	Rate/$[Mn^{III}]^{1\cdot10}$
2·60	7·3	571
3·19	8·8	582
3·84	10·3	589
4·35	11·7	580
4·99	13·2	583
5·71	14·7	592
6·19	16·1	584
6·83	17·6	581
7·38	19·1	571
8·22	20·5	591
8·85	22·0	590

Oxidations of Ethylmalonic and Benzylmalonic Acids by Manganic Pyrophosphate.— The oxidations of these two substituted acids were investigated in the hope that the elucidations of their reactions might, by analogy, help to clarify views concerning the secondary stages of both the ærobic and the anærobic oxidation of malonic acid, but since both substituted acids exhibit marked initial differences in behaviour from malonic acid an exhaustive experimental study has not been made.

Oxidations under nitrogen occur more rapidly with the substituted acids (Table 5) and are not affected by the addition of manganous ions. Again, methanol and ethanol have no effect on the rates of oxidation of the substituted acids, and do not produce solutions

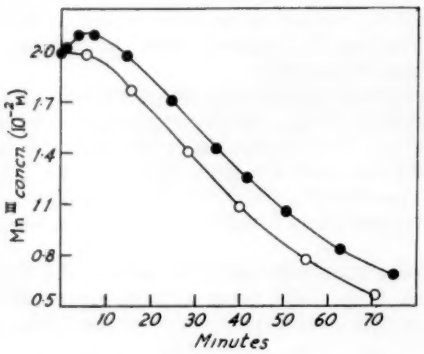
TABLE 5. *Comparative rates of oxidation of substituted malonic acids under nitrogen.*

pH 1·40; temp. 35·0°. Initial concns.: Mn^{III} 1·91 × 10^{-3}M; malonic acids 6·30 × 10^{-2}M; pyrophosphate 1·62 × 10^{-1}M.

	Decrease in concentration of Mn^{III} (M × 10^{-3})		
Time (min.)	Malonic acid	Ethylmalonic acid	Benzylmalonic acid
10	1·07	3·15	6·15
20	1·90	6·00	10·3
30	2·50	8·45	13·2
40	3·00	10·3	14·8

containing aldehydes. Evidently the radicals $(HO_2C)_2C(R)\cdot$ are much weaker oxidants when R = Et or CH_2Ph than when R = H. However vinyl cyanide, which polymerises, reduces the rates of these oxidations (again an effect opposite to that with malonic acid) so that the independent existence of the above radicals and their further oxidation by

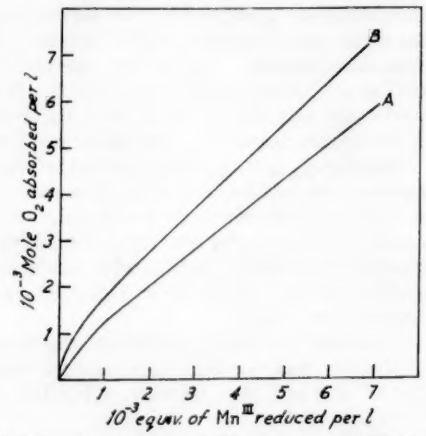
FIG. 6. *Oxidation of benzylmalonic acid under oxygen.*



pH 1·39; *temp.* 25·0°. *Initial concns.*: *benzylmalonic acid*, 6·59 × 10^{-2}M; Mn^{2+}, 5·38 × 10^{-3}M; *pyrophosphate*, 0·168M.

● *Iodometry.*
○ *Colorimetry.*

FIG. 7. *Oxidation of ethylmalonic acid under oxygen.*



pH 1·58; *temp.* 35·0°. *Initial concns.*: Mn^{III}, 1·07 × 10^{-2}M; *ethylmalonic acid*, 4·65 × 10^{-2}M; *pyrophosphate*, 0·123M.

A, No manganous sulphate added.
B, Initial concn. of manganous sulphate, 1·78 × 10^{-3}M.

Mn^{III} cannot be doubted. In prolonged oxidations of ethylmalonic acid as many as 6—7 equivalents of Mn^{III} can be consumed per mole of acid, which must thus be degraded in part beyond the stage of either methylpyruvic or propionic acid.

In the presence of oxygen the reduction of Mn^{III} by ethyl- and benzyl-malonic acid is retarded, and not accelerated. Moreover the addition of manganous sulphate then reduces the initial rate of reduction of Mn^{III} so much that there can be no doubt about the formation of hydroperoxides capable of oxidising Mn^{II} to Mn^{III}.

Fig. 6 which contrasts iodometric titrations with colorimetric measurements confirms this deduction for benzylmalonic acid, with which the thiosulphate titre even shows a slight increase during the first few minutes owing to the formation of a fairly constant amount of the hydroperoxide, $Ph\cdot CH_2\cdot C(O_2H)(CO_2H)_2$, which, as well as Mn^{3+}, is capable of oxidising I^- to I_2. Similar, but less pronounced, discrepancies between iodometric and colorimetric measurements have been observed with ethylmalonic acid. Comparative, oxygen uptake measurements with this substance (Fig. 7) show that the addition of manganous salt increases the ratio *R* (p. 2461), which at first has a very high value indicative of the presence of the hydroperoxide molecule $(HO_2C)_2C(Et)\cdot O\cdot OH$. After about 20 min.

R settles down to values somewhat below 1·0, as the hydroperoxide decomposes to products which are further oxidised by the manganic pyrophosphate. Though it is clear that the rates of formation and destruction of hydroperoxide are in balance for a long time no definite conclusions can, as yet, be drawn concerning the secondary reactions. Methanol and ethanol both retard slightly the rate of consumption of Mn^{III} in these ærobic oxidations.

The essential differences in behaviour between the unsubstituted and the substituted malonic acids in the presence of oxygen can be associated with the relative stabilities of substituted hydroperoxides, which are normally $R{\cdot}CH_2{\cdot}O{\cdot}OH < R_2CH{\cdot}O{\cdot}OH < R_2C{\cdot}O{\cdot}OH$. The electrophilic carboxyl groups of malonic acid must reduce the stability of the molecule $(HO_2C)_2CH{\cdot}O{\cdot}OH$ so much that its independent existence is in doubt, whereas the tertiary hydroperoxides $(HO_2C)_2CR{\cdot}O{\cdot}OH$, in which the electron-donating alkyl group partly neutralises the polar effect of the carboxyl group (see p. 2466), can certainly exist for periods of the order of minutes.

The effect of manganous salts on the ratio R can most simply be accounted for by the reaction sequence :

$$Mn^{III} + R{\cdot}CH(CO_2H)_2 \longrightarrow Mn^{II} + H^+ + (HO_2C)_2C(R)\cdot$$
$$(HO_2C)_2C(R)\cdot + O_2 \longrightarrow (HO_2C)_2C(R){\cdot}O{\cdot}O\cdot$$
$$(HO_2C)_2C(R){\cdot}O_2\cdot + Mn^{II} + H^+ \longrightarrow (HO_2C)_2C(R){\cdot}O{\cdot}OH + Mn^{III}$$

since there is little fall in Mn^{III} during the first few minutes in which the hydroperoxide concentration is building up to its equilibrium value (see Fig. 6).

This mechanism, which, corresponding to scheme (iii) for the ærobic oxidation of malonic acid, is an oxidation chain with respect to manganese ions, here seems to be more satisfactory than the usual chain reaction (scheme ii) in which the peroxy-radical is the hydrogen abstractor. Since however re-oxidation of Mn^{II} may be due to the subsequent peroxide decomposition

$$(HO_2C)_2C(R){\cdot}O{\cdot}OH + Mn^{3+} \longrightarrow (HO_2C)_2C(R){\cdot}O\cdot + Mn^{2+} + OH^- \quad . \quad . \quad (16)$$

scheme (ii) cannot be rejected decisively.

Oxidation of Malonic Acid by Potassium Permanganate.—The reduction of cold potassium permanganate by malonic acid at pH $\ll 1$ is preceded by a noticeable induction period (cf. Sanyal and Dhar, *Z. anorg. Chem.*, 1924, **139**, 161), but the later course of the oxidation becomes obscured by the separation of brown manganese dioxide though the Guyard reaction

$$2MnO_4^- + 3Mn^{2+} + 2H_2O = 5MnO_2 + 4H^+$$

Initial addition of manganous sulphate eliminates the induction period almost completely (Fig. 8, curve *B*) but hastens also the formation of manganese dioxide. Conversely the addition of either fluoride or pyrophosphate anions greatly prolongs the induction period (Fig. 8, curves *C* and *D*) and completely prevents separation of manganese dioxide. Since these anions act by forming complexes with Mn^{2+}, and more especially Mn^{3+}, it can be concluded that in dilute acid the MnO_4^- anion itself does not attack undissociated malonic acid; in alkali, however, oxidation of the malonate anion is rapid (see Part I). If, however, manganic pyrophosphate solution is added initially, the acid permanganate oxidation of malonic acid commences immediately (Fig. 8, curve *E*). Presumably the malonic acid is first attacked by the Mn^{III}, by the reactions elucidated in the preceding sections of this paper, and the resulting organic radical is then rapidly oxidised by a permanganate anion :

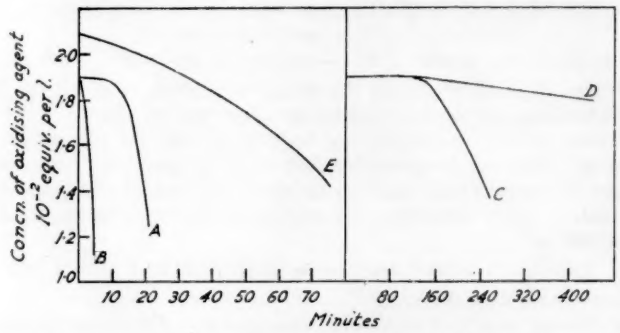
$$\cdot CH(CO_2H)_2 + MnO_4^- \longrightarrow {}^+CH(CO_2H)_2 + MnO_4^{2-} \quad . \quad . \quad . \quad . \quad . \quad (17)$$

Manganate anions thus formed would very rapidly yield more Mn^{III}, or possibly Mn^{IV}, by the Guyard reaction and the equilibration $Mn^{4+} + Mn^{2+} \rightleftharpoons 2Mn^{3+}$. The two anions which, in the absence of added manganic or manganous salt, prolong the initial induction period are those which remove Mn^{3+} ions as inactive complexes, but since this complex formation is a mobile equilibrium, and not an irreversible process, oxidations through reactions (7) and (8) will eventually occur autocatalytically. As would be expected the autocatalytic oxidation accelerates much more rapidly when pyrophosphate has not been added to the solution.

Oxygen has a slight retarding effect on the reduction of permanganate. Consequently reaction (17) must be fast, though not sufficiently so to prevent the oxygen from deviating a small part of the oxidation of the radical $\cdot CH(CO_2H)_2$ through the path of the ærobic sequence discussed on pp. 2457 and 2466. The latter oxidation must involve a series of reactions which are slower than the permanganate oxidation of the initial radical *via* tartronic and formic acid.

Some Comments on Oxidising and Reducing Powers of Free Radicals.—This investigation has provided a striking instance of a radical-transfer process (reaction 3, p. 2458) whereby one organic compound (malonic acid) can catalyse the oxidation of substances (alcohols, ethers) which are not directly attacked by the oxidising agent at hand (Mn^{III}). Mackinnon and Waters previously (*loc. cit.*) called attention to an oxidation (by $\cdot OH$) whereby a free radical could effect a subsequent reduction, and analgous induced hydrogen-transfers involving free thiyl radicals have been described by Bickel and Kooyman (*Nature*, 1952, **170**, 211), Harris and Waters (*ibid.*, p. 212), and Barrett and Waters (*Discuss. Faraday Soc.*, 1953,

FIG. 8. *Oxidations of malonic acid by potassium permanganate.*



All mixtures had initial concns. of $KMnO_4$ $3{\cdot}81 \times 10^{-3}$M *and of malonic acid* $1{\cdot}60 \times 10^{-2}$M. Temp. 20·0°.

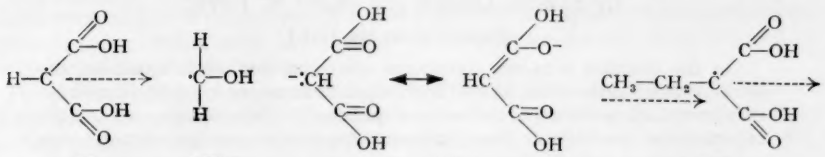
A, No added ions; pH 1·05.
B, Manganous sulphate ($3{\cdot}89 \times 10^{-3}$M) *added*; pH 1·05.
C, Potassium hydrogen fluoride ($4{\cdot}99 \times 10^{-2}$M) *added*; pH 1·35.
D, Sodium pyrophosphate ($1{\cdot}48 \times 10^{-2}$M) *added*; pH 0·96.
E, Manganic pyrophosphate (Mn^{III}, $2{\cdot}16 \times 10^{-3}$M) *added* (*pyrophosphate as in D*): pH 0·96.

14, 221). The concept (Mackinnon and Waters, *loc. cit.*) that two oxidation–reduction potentials, $E_{(-e)}$ and $E_{(+e)}$ may be assigned to any free radical provides a rational explanation of available facts more explicitly than the more recent, though similar, vague suggestion of Kharasch, Zimmermann, Zimmt, and Nudenberg (*J. Org. Chem.*, 1953, **18**, 1045).

Thus the fact that the initial oxidation of malonic acid by manganic pyrophosphate is reversible places $E_{(+e)}$ for the radical $\cdot CH(CO_2H)_2$ at about $+1{\cdot}1$ v under the conditions used. Since this radical can also be oxidised by manganic pyrophosphate, $E_{(-e)}$ must have a slightly lower value. The reducibility of the $\cdot CH(CO_2H)_2$ radical probably explains why malonic acid is not detectably oxidised by hydroxyl radicals and also why it is not autoxidised. Consistent too with this view is the fact that ethyl α-bromomalonate is a typical " positive halogen " compound (Robertson and Waters, *J.*, 1947, 492; Ford and Waters, *J.*, 1952, 2240).

As indicated by earlier suggestions of Merz and Waters (*loc. cit.*) both the $E_{(+e)}$ and the $E_{(-e)}$ values of free radicals depend on the spatial distribution of the odd electron within the radical structure. Thus for malonic acid radical (I) the inductive effect of the two carboxyl groups must bring about absorption of the odd electron into the molecule and so diminish the tendency to further electron loss to a much greater extent than in the alcohol radical (II); but this electron drift similarly enhances the tendency to electron gain whereby the resonance-stabilised anion (III) is formed. The added resonance stability of (III) also favours energetically the reaction (I) + e ⟶ (III).

The polar control of oxidation–reduction potentials of radicals is further exemplified by the different behaviours of ethyl- and benzyl-malonic acid: the electron-repelling ($+I$) alkyl groups tend to compensate for the loss of electron density at the point of free valency



(I) (II) (III) (IV)

due to the carboxyl groups and thereby diminish the oxidising powers of the radicals $(HO_2C)_2C(Alk)\cdot$ (IV), compared with (I).

Experimental

Materials.—Sodium manganic pyrophosphate solutions were prepared from "AnalaR" reagents as described in Part II. Malonic acid was recrystallised to constant m. p. (134°) from ether–benzene containing 5% of light petroleum (b. p. 40—60°); ethylmalonic (m. p. 112°) and benzylmalonic acids (m. p. 120°) were recrystallised from benzene. Sodium mesoxalate was prepared by the method of Chattaway and Harris (*J.*, 1922, 2703), and glyoxylic acid by that of Benedict (*J. Biol. Chem.*, 1909, **6**, 51).

Kinetic Measurements.—The reactions under nitrogen were carried out as described in Part III. With reactions in oxygen the rate of reduction of Mn^{III} was shown to be independent both of the rate of stirring and of the rate of flow of oxygen through the solution. All iodometric titrations were performed as rapidly as possible so as to minimise errors due to dissolution of oxygen. Colorimetric measurements of Mn^{III} were made by the standard method with a "Spekker" photo-electric absorptiometer with a green (No. 604) filter. Rates of absorption of oxygen were measured, by the standard procedure (Milton and Waters "Quantitative Micro-analysis," Ed. Arnold & Co., London, 1949), in Warburg micro-respirometers, shaken at 35°, at 130 oscillations per minute. Filter paper saturated with 20% potassium hydroxide solution was placed in the central cups of the reaction vessels to absorb the carbon dioxide evolved during the reaction. The buffered manganic pyrophosphate solution was placed in the main reaction vessel, and a known excess of malonic acid solution in the side-arm. Every determination was repeated at least 3 times.

Induced Polymerisation.—The polyvinyl cyanide formed during the anærobic oxidation of malonic acid in presence of vinyl cyanide was washed 12 times with distilled water at the centrifuge and was then dried at 100°. The infra-red spectrum showed, besides the very strong CN absorption band at 4·5 μ, distinct absorptions at 3·01 μ (OH group) and at 5·81 and 5·96 μ (C=O) which confirm the presence of carboxyl groups at the ends of the polymer chains.

Identification of Oxidation Products.—Formic acid, from the anærobic oxidations of malonic, tartronic, and glyoxylic acids was separated from the dilute aqueous reaction mixtures by passing a slow stream of air through warmed solutions and freezing their vapours in carbon dioxide–ethanol traps. The collected liquids gave chromotropic acid reactions for formic acid (Feigl, "Spot Tests," Elsevier, Amsterdam, 1949, p. 397).

Induced Oxidations.—The anærobic oxidation of malonic acid by manganic pyrophosphate in the presence of manganous ions was accelerated by the compounds listed in Table 1 (p. 2458). The following factors indicate the extent of acceleration of the initial reaction at pH 1·08 of mixtures of 100 ml. of 0·0243N-manganic pyrophosphate, 10 ml. of M-malonic acid, and 5 ml. of solutions containing 0·025 moles of added substrate: formic acid 1·5, diethyl ether 2·1, vinyl cyanide 3·3, ethanol 3·7, *iso*propanol 4·9, maleic and fumaric acid 26 times. Volatile oxidation products were separated by a stream of air, as described above; aldehydes were characterised by the m. p. and mixed m. p. of their dimedone derivatives, and other products were identified by diagnostic spot tests.

We thank the Royal Society for a grant for the purchase of a "Spekker" photo-absorptiometer. One of us (A. Y. D.) thanks the Department of Scientific & Industrial Research for a Maintenance Grant.

Dyson Perrins Laboratory, Oxford. [*Received, January 21st*, 1954.]

The Reduction of Anthraquinone and other Polycyclic Quinones with Aluminium Alkoxides (Meerwein–Pondorff Reagent).

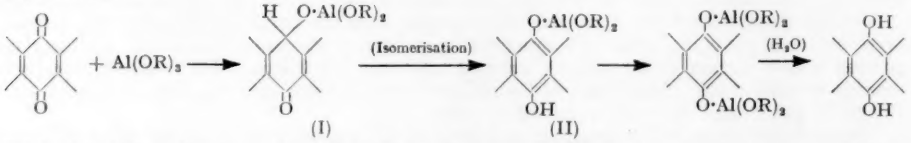
By Samuel Coffey and (Miss) V. Boyd.

[Reprint Order No. 5119.]

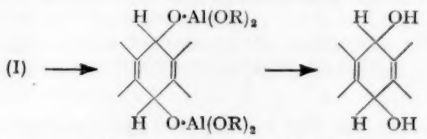
In the reaction between aluminium alkoxides and anthraquinones the corresponding anthracene, 9 : 10-dihydroxyanthracene, or 9 : 10-dihydro-9 : 10-dihydroxyanthracene may be obtained depending on the alkoxide used and the experimental conditions. From nitroanthraquinones, aminoanthraquinones are first formed and these may react further with the products obtained from the oxidation of the alkoxide; 1-amino-2-methylanthraquinone affords 2 : 4-dimethyl-3-azabenzanthrone. 1 : 5-Dichloroanthraquinone cannot be reduced beyond the dihydrodihydroxyanthracene stage. Anthanthrone and flavanthrone are reduced to anthanthrene and flavanthrene respectively.

The Meerwein–Pondorff reaction for reducing aldehyde and keto-groups to primary and secondary alcoholic groups respectively by treatment with an aluminium alkoxide has been studied for a wide range of compounds (cf. " Organic Reactions," Vol. II, p. 178, John Wiley & Son Inc., New York, 1944), but it has only recently been applied to an aromatic polycyclic ketone. By treating *meso*benzanthrone and anthrone respectively with aluminium *iso*propoxide in *iso*propanol, Campbell and Woodham (*J.*, 1952, 843) obtained benzanthrene in 75% and anthracene in quantitative yield, the reduction proceeding further than the expected alcohol stage and so becoming irreversible. As far as can be ascertained, there is no mention in the literature of the reaction having been studied with polycyclic quinones, although it is recorded that benzoquinone is reduced to quinol. According to Boyland and Manson (*J.*, 1951, 1837) anthraquinone is converted into 9 : 10-dihydro-9 : 10-dihydroxyanthracene and 1 : 4-naphthaquinone into 1 : 2 : 3 : 4-tetrahydro-1 : 4-dihydroxynaphthalene and 1 : 2 : 3 : 4-tetrahydro-4-hydroxy-1-oxonaphthalene by reduction with lithium aluminium hydride, which often gives a similar result to the Meerwein–Pondorff reaction.

The reduction of anthraquinone and a number of its derivatives by a series of aluminium alkoxides has now been studied. From anthraquinone the reaction produces 9 : 10-dihydroxyanthracene, 9 : 10-dihydro-9 : 10-dihydroxyanthracene, or anthracene according to the alkoxide employed. Alkoxides of lower primary alcohols, *e.g.*, the ethoxide and *n*-butoxide, give only 9 : 10-dihydroxyanthracene. In these cases probably only one keto-group in the anthraquinone molecule is involved in the initial reaction which may be represented as :



With aluminium *iso*propoxide, which is a more powerful reducing agent, the second keto-group in (I) also reacts, leading to the formation of the alkoxide of 9 : 10-dihydro-9 : 10-dihydroxyanthracene, as normally expected from a Meerwein–Pondorff reduction :



9 : 10-Dihydroxyanthracene is not reduced to 9 : 10-dihydro-9 : 10-dihydroxyanthracene by this reagent so that, as expected, it is probably the keto-group in (I) which is attacked.

With the higher-boiling butanols, particularly with butan-2-ol, the 9 : 10-dihydro-9 : 10-dihydroxyanthracene is reduced a stage further to give anthracene, and with aluminium

tri(*cyclo*hexyl oxide) in *cyclo*hexanol 9 : 10-dihydroxyanthracene also is reduced to the hydrocarbon. 1-Chloro- and 1 : 5-dichloro-anthraquinone could not be reduced beyond the dihydrodihydroxyanthracene stage.

In nitroanthraquinones the nitro-group appears to be reduced before the keto-group, which is unusual in this type of reaction, and 1-amino-2-methylanthraquinone preferentially undergoes condensation with *iso*propanol (or the acetone formed by oxidation) to form 2 : 4-dimethyl-3-azabenzanthrone.

The polynuclear quinones anthanthrone and flavanthrone are reduced to anthanthrene and flavanthrene respectively. Thus this method of converting quinones into the corresponding hydrocarbons is a reasonable alternative to that of Clar (*Ber.*, 1934, **67**, 1229) using zinc and zinc chloride but, in the cases investigated, shows no marked advantage.

Experimental

Preparation of Various Aluminium Alkoxides.—The alcohol was dried by distillation over calcium oxide or calcium carbide. In most experiments the following procedure was adopted: the alcohol (100 c.c.) and aluminium turnings (5 g.) were boiled under a reflux condenser fitted with a calcium chloride tube. A trace of mercuric chloride and dry carbon tetrachloride (1 c.c.) were added to catalyse the reaction and the mixture refluxed overnight (all the aluminium had then reacted), leaving a slight grey precipitate in a clear solution which was used without further treatment.

Reductions of Anthraquinone.—(*a*) *With aluminium* iso*propoxide.* Aluminium *iso*propoxide solution (100 c.c.), anthraquinone (10 g.), and *iso*propanol (50 c.c.) were refluxed together for 48 hr. The excess of *iso*propanol was distilled off and the residue poured into 3% aqueous sodium hydroxide (500 c.c.). The deep red aqueous alkaline solution of 9 : 10-dihydroxyanthracene was filtered. The residue, consisting of hydrated alumina and organic material, was stirred with a little alkaline dithionite solution to remove any anthraquinone remaining unchanged or reformed by atmospheric oxidation of 9 : 10-dihydroxyanthracene, and was extracted with benzene.

The aqueous filtrate oxidised rapidly and gave a precipitate of anthraquinone which was taken as a measure of the yield of 9 : 10-dihydroxyanthracene. The benzene extract on evaporation gave colourless needles (4·4 g.), m. p. ~160°. The yield of 9 : 10-dihydroxyanthracene was approximately equal to that of the colourless reduction product. The experiment was repeated using 200 and 400 c.c. of aluminium *iso*propoxide solution, but in each case similar yields were obtained. When less than 100 c.c. of alkoxide solution was used a lower yield of the colourless reduction product and a higher yield of 9 : 10-dihydroxyanthracene were obtained.

The colourless reduction product was 9 : 10-dihydro-9 : 10-dihydroxyanthracene (Found: C, 79·4; H, 6·0. Calc. for $C_{14}H_{12}O_2$: C, 79·3; H, 5·7%); the diacetyl derivative (prepared by treatment with acetic anhydride in pyridine on a water-bath for 6 hr.) had m. p. 175° (from alcohol) (Found: C, 72·7; H, 5·7. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·4%).

A mixture of the reduction product (0·5 g.), pyridine (5 c.c.), and benzoyl chloride (5 c.c.) was kept at room temperature for 24 hr., then poured into water and extracted with benzene. A brown oil, which solidified on long standing, was obtained, which was dissolved in alcohol and treated with charcoal. The dibenzoyl derivative was obtained as colourless needles, m. p. 145° (Found: C, 80·1; H, 4·7%. Calc. for $C_{28}H_{20}O_4$: C, 80·0; H, 4·8%).

The individual *cis*- and *trans*-9 : 10-dihydro-9 : 10-dihydroxyanthraquinones (it may also exist in polymorphic forms) and its derivatives have not yet been characterised satisfactorily. Boyland (*loc. cit.*) isolated two forms (needles, m. p. 140°, and plates, m. p. 137°) and one dibenzoate (m. p. 127—128°); Prevost (*Compt. rend.*, 1935, **200**, 408) describes the parent compound, prepared from anthracene, as flexible needles, m. p. 150—180° (very indefinite) (benzoate, m. p. 127—128°), and Dufraisse and Houpillart (*Compt. rend.*, 1937, **205**, 740) have described a compound prepared by reducing anthracene photo-oxide having a very indefinite maximum m. p. ~195°.

(*b*) *With aluminium* n-*butoxide.* 9 : 10-Dihydroxyanthracene only was present after anthraquinone (10 g.) had been boiled in aluminium *n*-butoxide solution [aluminium (5 g.) in butanol (150 c.c.)] for 48 hr.

(*c*) *With aluminium* sec.-*butoxide.* When the above experiment was repeated using aluminium *sec.*-butoxide in butan-2-ol, anthracene (4·2 g.) separated as flat platelets, m. p. 218° (Found: C, 94·4; H, 6·1. Calc. for $C_{14}H_{10}$: C, 94·4; H, 5·6%), on evaporation of the benzene extract. Anthraquinone (present as 9 : 10-dihydroxyanthracene) (3·6 g.) was recovered from the aqueous alkaline dithionite liquor.

(*d*) *With aluminium* iso*butoxide*. With aluminium *iso*butoxide in *iso*butanol, anthracene (1 g.) was obtained, the remainder being 9 : 10-dihydroxyanthracene.

(*e*) *With aluminium tri*(cyclo*hexyl oxide*). Anthraquinone (10 g.), aluminium tri(*cyclo*hexyl oxide) solution (100 c.c.), and *cyclo*hexanol (50 c.c.) were refluxed for 48 hr., and poured into water. Sufficient benzene was added to give a clear upper layer. The mixture was filtered and the residue extracted with benzene. The combined benzene extracts on steam-distillation afforded 6·8 g. of anthracene. This appeared to be the sole product, but it was not easy to isolate it quantitatively from the *cyclo*hexanol also present.

(*f*) *With aluminium ethoxide*. The sole product was 9 : 10-dihydroxyanthracene.

Reduction of 9 : 10-*Dihydroxyanthracene*.—When anthraquinone was replaced by 9 : 10-dihydroxyanthracene, no further reduction occurred with aluminium *iso*propoxide over a wide range of concentrations, but by using aluminium tri(*cyclo*hexyl oxide) a quantitative yield of anthracene was obtained from both 9 : 10-dihydroxyanthracene and 9 : 10-dihydro-9 : 10-dihydroxyanthracene.

Reduction of 1 : 5-*Dichloroanthraquinone*.—Aluminium *iso*propoxide solution (100 c.c.), 1 : 5-dichloroanthraquinone (14 g.), and *iso*propanol (50 c.c.) were refluxed for 48 hr., the excess of alcohol was removed, and the product poured into dilute alkali to give a pale red solution and the usual precipitate, which was filtered off. The dried residue was extracted with benzene, 1 : 5-dichloroanthraquinone was removed by treatment with warm, alkaline sodium dithionite solution, and the remaining product, when crystallised from benzene, gave mainly *trans*-1 : 5-dichloro-9 : 10-dihydro-9 : 10-dihydroxyanthracene (4·5 g.), m. p. 220—224° (cf. Barnett, Cook, and Matthews, *Rec. Trav. chim.*, 1925, **44**, 728; *Ber.*, 1925, **58**, 975) (Found : C, 59·1; H, 4·0; Cl, 25·1. Calc. for $C_{14}H_{10}O_2Cl_2$: C, 59·7; H, 3·6; Cl, 25·2%). The diacetyl derivative, m. p. 247—248°, crystallised from benzene (Barnett *et al.*, *loc. cit.*, give 249°) (Found : C, 59·4; H, 4·1; Cl, 19·9. Calc. for $C_{18}H_{14}O_4Cl_2$: C, 59·2; H, 3·8; Cl, 19·5%).

When the experiment was repeated using aluminium tri(*cyclo*hexyl oxide) solution the dichlorodihydroxyanthracene (6 g.; m. p. 205·9°) consisted mainly of the *cis*-compound as judged from its m. p.

Reduction of 1-*Chloroanthraquinone*.—This reaction in aluminium *iso*propoxide solution afforded 1-*chloro*-9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene* as colourless needles (5·6 g.), m. p. 178° (Found : C, 69·2; H, 4·6; Cl, 14·8. $C_{14}H_{11}O_2Cl$ requires C, 68·1; H, 4·5; Cl, 14·4%). The *diacetyl* derivative, colourless needles from ethanol, had m. p. 160° (Found : C, 64·8; H, 4·5; Cl, 11·1. $C_{18}H_{15}O_4Cl$ requires C, 65·4; H, 4·5; Cl, 10·8%). A similar result was obtained with aluminium tri(*cyclo*hexyl oxide) in *cyclo*hexanol.

Reduction of 1-*Amino*-2-*methylanthraquinone*.—*Preparation of* 2 : 4-*dimethyl*-3-*azabenzanthrone*. 1-Amino-2-methylanthraquinone (10 g.), aluminium *iso*propoxide solution (100 c.c.), and *iso*propanol (50 c.c.) were refluxed for 48 hr., the excess of alcohol was removed, and the residue poured into water. The dried precipitate when extracted with benzene gave red-brown needles (7·6 g.), m. p. 248°. Traces of unchanged 1-amino-2-methylanthraquinone were removed by treatment with alkaline sodium dithionite solution and the product was recrystallised from ethyl acetate as almost colourless crystals, m. p. 254°, of 2 : 4-*dimethyl*-3-*azabenzanthrone*, m. p. 254° (Found : C, 82·8; H, 5·2; N, 5·6. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0; N, 5·4%). The product could not be acetylated.

The same compound was obtained by refluxing 1-amino-2-methylanthraquinone (5 g.), *iso*propanol (100 c.c.), acetone (10 c.c.), and aqueous sodium hydroxide (3·3 g. of NaOH in 6·7 c.c. of water) overnight.

Reduction of 2-*Methyl*-1-*nitroanthraquinone*.—2-Methyl-1-nitroanthraquinone (10 g.), aluminium *iso*propoxide solution (100 c.c.), and *iso*propanol (50 c.c.) yielded 1-amino-2-methylanthraquinone, the nitro-group being reduced preferentially. When three times as much *iso*propoxide solution was used, 2 : 4-dimethyl-3-azabenzanthrone was formed. Reductions of 1-nitro- and 1-amino-anthraquinones gave very complex mixtures.

Reductions of Higher Polycyclic Quinones.—Aluminium tri(*cyclo*hexyl oxide) solution (100 c.c.) and anthanthrone (6 g.) were refluxed for 48 hr., and worked up as usual. Extraction with benzene gave 1·5 g. of anthanthrene as yellow-green leaflets, m. p. 258° (Found : C, 94·8; H, 4·8. Calc. for $C_{22}H_{12}$: C, 95·5; H, 4·5%), identified by comparison with an authentic specimen. Similar reduction of flavanthrone gave flavanthrene (Found : C, 89; H, 3·7; N, 7·1. Calc. for $C_{28}H_{12}N_2$: C, 88·4; H, 4·2; N, 7·4%), also identified by comparison with an authentic specimen.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, DYESTUFFS DIVISION,
RESEARCH DEPARTMENT, BLACKLEY, MANCHESTER 9. [*Received, February* 13*th*, 1954.]

Internuclear Cyclisation. Part IX. Abnormal Reactions of 2-Amino-*N*-methylbenzanilides containing* ortho-*Substituents.*

By D. H. Hey and D. G. Turpin.

[Reprint Order No. 5168.]

Decomposition of diazonium salts prepared from 2-amino-*N*-methylbenzanilides which contain a substituent atom or group at the *meta*- or *para*-position with reference to the nitrogen atom gives rise to *N*-methylphenanthridones, but with a substituent atom or group at the *ortho*-position the reaction gives a substituted benzanilide by a process of deamination and demethylation. *N*-Methylphenanthridones have been prepared from 2-amino-*N*-methylbenzo-2′-naphthalide, 2-amino-4′-methoxycarbonyl-*N*-methylbenzanilide, and 2-amino-3′-carboxy-*N*-methylbenzanilide, but deamination and demethylation took place with 2-amino-*N*-methylbenzo-1′-naphthalide, 2-amino-2′-methoxycarbonyl-*N*-methylbenzanilide, 2-amino-2′-carboxy-*N*-methylbenzanilide, 2-amino-*N*-methylbenzo-*o*-toluidide, 2-amino-2′-chloro-*N*-methylbenzanilide, 2-amino-*N*-methyl-2′-nitrobenzanilide, 2-amino-2′ : 4′ : *N*-trimethylbenzanilide, and 2-amino-2′-ethyl-*N*-methyl-4 : 5-methylenedioxybenzanilide.

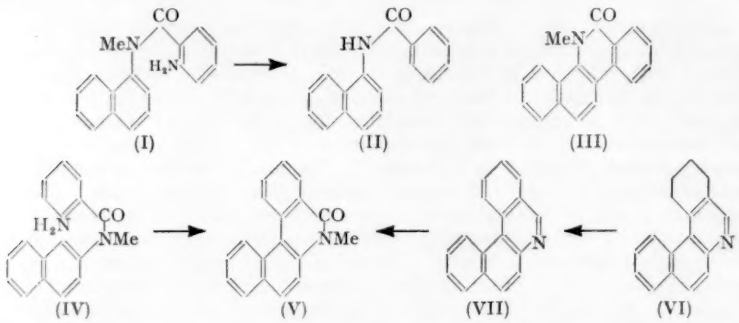
It has been shown in Parts III, VI, and VII (*J.*, 1952, 1508, 4059; 1953, 3) that diazonium salts of *o*-amino-*N*-methylbenzanilides can be readily converted into *N*-methylphenanthridones. The success so far achieved suggested that similar reactions on appropriate derivatives of benzo-1-naphthalide might provide a new approach to the synthesis of alkaloids of the chelidonine–sanguinarine group, which contain the 1 : 2-benzophenanthridine system. A somewhat similar approach was envisaged by Richardson, Robinson, and Seijo (*J.*, 1937, 835), who attempted to apply a Pschorr-type ring closure to the reduction product of the Schiff base prepared from 6-nitropiperonaldehyde and α-naphthylamine, but diazotisation afforded only a brown tar. The failure of a similar reaction was reported by Noller, Denyes, Gates, and Wasley (*J. Amer. Chem. Soc.*, 1937, **59**, 2079). Forrest, Haworth, Pinder, and Stevens (*J.*, 1949, 1311) were unable to obtain any product from diazotised 2-amino-*N*-methyl-4 : 5-methylenedioxybenzo-1′-naphthalide, although they reported the formation of *N*-methyl-6 : 7-methylenedioxyphenanthridone in more than 50% yield by heating the diazonium sulphate prepared from 2-amino-*N*-methyl-4 : 5-methylenedioxybenzanilide.

N-Methyl-2-nitrobenzo-1′-naphthalide has now been prepared from (*a*) α-naphthylamine and *o*-nitrobenzoyl chloride with subsequent methylation and (*b*) *N*-methyl-α-naphthylamine and *o*-nitrobenzoyl chloride, and reduced catalytically to 2-amino-*N*-methylbenzo-1′-naphthalide (I). This amine was converted into the diazonium fluoroborate (cf. Part III, *loc. cit.*), which was decomposed in suspension in acetone by the addition of copper powder. From this reaction there were obtained (*a*) benzo-1-naphthalide (II), (*b*) a compound, m. p. 178—179°, and (*c*) a compound, m. p. 255—256°. In a similar decomposition of the diazonium sulphate the same three products were obtained, thus showing that the fluoroborate anion had no major influence on the products formed. Neither compound (*b*) nor compound (*c*) corresponded with the expected *N*-methyl-1 : 2-benzophenanthridone (III).

The non-formation of the phenanthridone and the unexpected appearance of benzo-1-naphthalide (II), the product of deamination and demethylation of the original 2-amino-*N*-methylbenzo-1′-naphthalide (I), suggested that a similar series of reactions on the corresponding derivatives of β-naphthylamine would be of interest. Accordingly, 2-amino-*N*-methylbenzo-2′-naphthalide (IV) was prepared in the same ways as its isomer. Decomposition of the diazonium fluoroborate prepared from it gave *N*-methyl-3 : 4-benzophenanthridone (V), together with a small amount of a compound, m. p. 180—181°.

* Part VIII, *J.*, 1954, 1697.

Theoretically, this ring closure could give *N*-methyl-3 : 4- or -2 : 3-benzophenanthridone (or a mixture of both), but the identity of the product as the former was demonstrated by an independent synthesis from 5 : 6 : 7 : 8-tetrahydro-3 : 4-benzophenanthridine (VI). This compound, which had been prepared by Hollingsworth and Petrow (*J.*, 1948, 1540), was dehydrogenated to give 3 : 4-benzophenanthridine (VII), converted into its methiodide and then oxidised with potassium ferricyanide to *N*-methyl-3 : 4-benzophenanthridone (V).

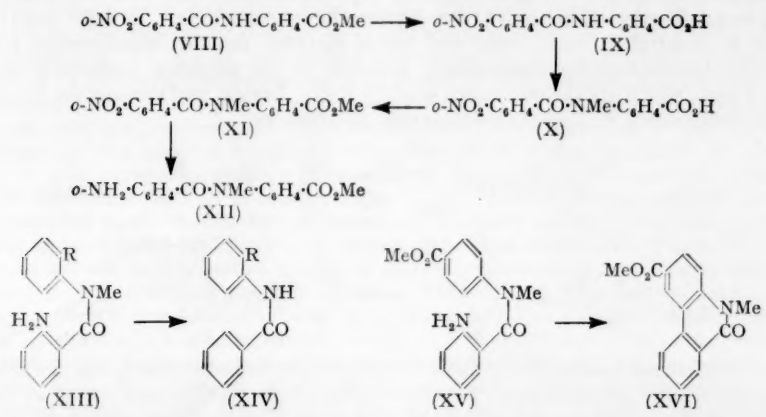


A parallel series of reactions was carried out on 2-amino-*N*-methylbenzanilides with a carboxy- or methoxycarbonyl group in the aniline nucleus. 2'-, 3'-, and 4'-Methoxycarbonyl-2-nitrobenzanilide (VIII), prepared from *o*-nitrobenzoyl chloride and the methyl ester of the appropriate aminobenzoic acid, on alkaline hydrolysis gave the corresponding carboxy-2-nitrobenzanilides (IX). The same acids were obtained from *o*-nitrobenzoyl chloride and the appropriate aminobenzoic acids (cf. Schroeter and Eisleb, *Annalen*, 1909, **367**, 128). Methylation of the carboxynitrobenzanilides (IX) with methyl sulphate gave the corresponding carboxy-*N*-methyl-2-nitrobenzanilides (X). 2'- and 4'-Carboxy-*N*-methyl-2-nitrobenzanilide in turn were esterified with methanol and hydrogen chloride to give 2'- and 4'-methoxycarbonyl-*N*-methyl-2-nitrobenzanilide (XI). Catalytic reduction of these two esters gave 2-amino-2'- and 2-amino-4'-methoxycarbonyl-*N*-methylbenzanilide (XII). Reduction of 2'-carboxy-*N*-methyl-2-nitrobenzanilide with ammoniacal ferrous sulphate gave either 2-amino-2'-carboxy-*N*-methylbenzanilide or 2'-carboxy-2-methylaminobenzanilide, depending on the experimental conditions used. The former is converted into the latter when heated above its melting point (182°). Catalytic reduction of 4'-carboxy-*N*-methyl-2-nitrobenzanilide gave 2-amino-4'-carboxy-*N*-methylbenzanilide.

Decomposition with copper powder of the aqueous diazonium sulphate prepared from 2-amino-2'-methoxycarbonyl-*N*-methylbenzanilide (XIII; R = CO_2Me) gave (*a*) methyl *N*-benzoylanthranilate (XIV; R = CO_2Me), (*b*) a compound, m. p. 259° (decomp.), and (*c*) a compound, m. p. 197°. On the other hand, a similar reaction on 2-amino-4'-methoxycarbonyl-*N*-methylbenzanilide (XV) gave 3-methoxycarbonyl-*N*-methylphenanthridone (XVI) and a trace of a compound of m. p. 232—234°. The application of the same reaction to 2-amino-2'-carboxy-*N*-methylbenzanilide (XIII; R = CO_2H), as the diazonium chloride or sulphate, gave *N*-benzoylanthranilic acid (XIV; R = CO_2H) and a compound, m. p. 303—304°. The latter product was also obtained on hydrolysis of the compound, m. p. 197°, obtained above in the corresponding reaction with the diazonium sulphate from 2-amino-2'-methoxycarbonyl-*N*-methylbenzanilide. Decomposition of the diazonium sulphate prepared from 2-amino-4'-carboxy-*N*-methylbenzanilide gave only a highly insoluble product, m. p. 341—343°, whereas decomposition of the diazonium chloride prepared from the reduction product of 3'-carboxy-*N*-methyl-2-nitrobenzanilide gave a mixture of 2- and 4-carboxy-*N*-methylphenanthridone, together with a second compound, m. p. 320—322°.

The results thus obtained in the decomposition of the diazonium salts prepared from the carboxy- and methoxycarbonyl derivatives of 2-amino-*N*-methylbenzanilide show that when the substituent is at the *ortho*-position with reference to the nitrogen atom an abnormal reaction results which consists of a process of deamination and demethylation.

When, however, the substituent is attached to either the *meta*- or the *para*-position the normal reaction leading to phenanthridone formation takes place. These results are analogous to those reported above with derivatives of α- and β-naphthylamine.



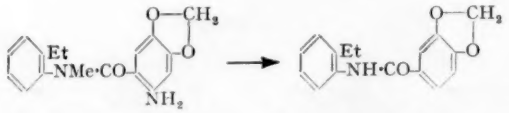
The occurrence of this abnormal reaction with *ortho*-substituted 2-amino-*N*-methylbenzanilides made it necessary to re-examine the three reactions reported in Parts VI and VII (*loc. cit.*) in which *ortho*-substituted benzanilides were used. The relevant bases are 2-amino-*N*-methylbenzo-*o*-toluidide (XIII; R = Me), 2-amino-2′-chloro-*N*-methylbenzanilide (XIII; R = Cl), and 2-amino-*N*-methyl-2′-nitrobenzanilide (XIII; R = NO_2). With the derivatives of *o*-toluidine and *o*-nitroaniline it was reported that the products were 1 : 10-dimethylphenanthridone, m. p. 141—142° (Found : C, 80·3; H, 6·1. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8%), and 10-methyl-1-nitrophenanthridone, m. p. 92—93° (Found : C, 65·5; H, 4·2. $C_{14}H_{10}O_3N_2$ requires C, 66·1; H, 3·9%) respectively. It is now shown that these two compounds are in fact benzo-*o*-toluidide (XIV; R = Me), m. p. 142—143° ($C_{14}H_{13}ON$ requires C, 79·6; H, 6·2%), and *o*-nitrobenzanilide (XIV; R = NO_2), m. p. 94° ($C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·1%), respectively. In the decomposition of the diazonium sulphate from 2-amino-2′-chloro-*N*-methylbenzanilide (XIII; R = Cl) no phenanthridone formation was reported, but an unidentified compound, m. p. 70—75° (Found : C, 67·4; H, 4·1; Cl, 15·3%), was isolated which would now appear to be impure *o*-chlorobenzanilide (XIV; R = Cl), m. p. 99° ($C_{13}H_{10}ONCl$ requires C, 67·4; H, 4·3; Cl, 15·2%). On the other hand, the products obtained from 2-amino-*N*-methylbenzanilide substituted at the *meta*- and the *para*-positions are phenanthridones.

The apparent general character of the abnormal reaction for 2-amino-*N*-methylbenzanilides substituted at the *ortho*-position with respect to the nitrogen atom made it necessary to reinvestigate two further reactions reported by other workers. First, Chardonnens and Würmli (*Helv. Chim. Acta*, 1950, **33**, 1340) have reported the formation of 1 : 3 : 10-trimethylphenanthridone, m. p. 194°, from the diazonium chloride prepared from 2-amino-2′ : 4′ : *N*-trimethylbenzanilide (XVII). This reaction has now been repeated and is found to give 2 : 4-dimethylbenzanilide (XVIII), m. p. 193—194°. No phenanthridone was obtained. Secondly, Kelly, Taylor, and Wiesner (*J.*, 1953, 2094) have reported the preparation of 1-ethyl-10-methyl-6 : 7-methylenedioxyphenanthridone, in crude form as a yellow wax, from the decomposition of the diazonium sulphate prepared from 2-amino-2′-ethyl-*N*-methyl-4 : 5-methylenedioxybenzanilide (XIX). The crude phenanthridone was reduced with lithium aluminium hydride to 1-ethyl-9 : 10-dihydro-10-methyl-6 : 7-methylenedioxyphenanthridine, which gave a picrate, m. p. 175°, and was stated to be identical with dihydrolycorineanhydromethine. This reaction has been repeated, following closely the experimental conditions described by Kelly, Taylor, and Wiesner (*loc. cit.*). The sole crystalline product isolated from this reaction was 2′-ethyl-3 : 4-methylenedioxybenzanilide (XX), m. p. 143—144°, identical with an authentic

specimen prepared from *o*-ethylaniline and 3 : 4-methylenedioxybenzoyl chloride. Reduction of this anilide with lithium aluminium hydride gave 2′-ethyl-3 : 4-methylenedioxybenzylaniline as an oil, which formed a picrate, m. p. 125°.

It is difficult to provide a satisfactory explanation for these two conflicting results with 2-amino-2′-ethyl-*N*-methyl-4 : 5-methylenedioxybenzanilide. In both reactions the product is isolated in small yield and much material remains unaccounted for. The 2′-ethyl-3 : 4-methylenedioxybenzanilide isolated by us sublimes unchanged at 130—150°/0·1 mm., which are the conditions used by Kelly, Taylor, and Wiesner for the isolation of 1-ethyl-10-methyl-6 : 7-methylenedioxyphenanthridone.

(XVII) (XVIII)

(XIX)  (XX)

The conclusions reached from these investigations indicate that in the decomposition of diazonium salts prepared from 2-amino-*N*-methylbenzanilides substituted at the *ortho*-position, the normal cyclisation process leading to an *N*-methylphenanthridone is replaced by a reaction involving *simultaneous deamination and demethylation.* The eight substituents studied are Me, Cl, NO_2, CO_2H, CO_2Me, 2 : 4-Me_2, Et, and α-naphthyl. It is of interest that this abnormal reaction appears to be substantially independent of both the polar character of the *ortho*-substituent and the experimental conditions of the decomposition, at least as far as these have been studied. The fundamental reason for the anomalous course of the reaction with *ortho*-substituents is considered to be steric. The enforced proximity of the *N*-methyl group to the diazonium group results in the replacement of the latter by hydrogen supplied by the methyl group. Relevant to these considerations appears to be the mobility of the methyl group (*a*) in the reduction of 2′-carboxy-*N*-methyl-2-nitrobenzanilide to 2′-carboxy-2-methylaminobenzanilide reported above, (*b*) the reduction of *N*-methyl-2 : 2′-dinitrodiphenylamine to 2-methylamino-2′-nitrodiphenylamine (Hey and Mulley, *J.*, 1952, 2287), and (*c*) the formation of 2 : 4′-dinitrodiphenylamine as one of the products of decomposition of the diazonium sulphate prepared from 2-amino-*N*-methyl-2′-nitrodiphenylamine. In the last-named reaction deamination and demethylation take place, accompanied by incidental nitration at the 4′-position arising from the presence of a nitrating entity in the reaction system. None of these observations is found in the absence of a substituent group at the *ortho*-position with reference to the nitrogen atom.

Experimental

N-Methyl-2-nitrobenzo-1′-naphthalide.—(*a*) An ethereal solution of *o*-nitrobenzoyl chloride, prepared from the acid (10 g.) by Boëtius and Romisch's method (*Ber.*, 1935, **68**, 1924), was added slowly to a solution of 1-naphthylamine (10 g.) in pyridine (15 c.c.) and dry ether (40 c.c.), and the solution was boiled under reflux for 1 hr. After removal of the ether, the mixture was poured into water. Recrystallisation from alcohol (charcoal) of the brown solid which separated gave *2-nitrobenzo-1′-naphthalide* (14·6 g.) in fluffy needles, m. p. 206° (Found : C, 70·0; H, 4·1. $C_{17}H_{12}O_3N_2$ requires C, 69·9; H, 4·1%). A solution of this compound (14·6 g.) in a mixture of acetone (90 c.c.) and 10% aqueous sodium hydroxide (90 c.c.) was boiled under reflux and methyl sulphate (25 c.c.) was added dropwise. The mixture was cooled and poured into 5% aqueous sodium hydroxide (600 c.c.). The solid which separated was recrystallised from benzene–light petroleum (b. p. 60—80°), to give *N*-methyl-2-nitrobenzo-1′-naphthalide (12·6 g.) in pale yellow diamond-shaped plates, m. p. 182—183° (Found : C, 70·9; H, 4·8. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6%). (*b*) *N*-Methyl-1-naphthylamine (0·5 g.) (Fischer, *Annalen*, 1895, **286**, 159) and *o*-nitrobenzoyl chloride (0·5 g.) in dry ether (40 c.c.), to which anhydrous potassium carbonate (1·5 g.) was added, were boiled under reflux for 10 min. and the ether removed. Addition of water gave a yellow solid, which on crystallisation from benzene–light petroleum

(b. p. 60—80°) gave *N*-methyl-2-nitrobenzo-1′-naphthalide (0·6 g.), m. p. 182—183°, identical with the compound prepared by method (*a*).

N-*Methyl*-2-*nitrobenzo*-2′-*naphthalide*.—(*a*) By the procedure (*a*) described above, 2-naphthylamine (10 g.) and *o*-nitrobenzoyl chloride (from 10 g. of acid) gave 2-*nitrobenzo*-2′-*naphthalide* (12·5 g.) in needles, m. p. 178—179°, from alcohol (charcoal) (Found: C, 70·0; H, 4·1%). Methylation of this compound (10·8 g.), as in the preceding example, gave N-*methyl*-2-*nitrobenzo*-2′-*naphthalide* (7·1 g.) in pale yellow prisms, m. p. 110—111°, from benzene–light petroleum (b. p. 40—60°), which darkened on exposure to light (Found: C, 70·6; H, 4·7%). (*b*) A solution of *N*-toluene-*p*-sulphon-2-naphthalide (21·3 g.) (Morgan and Micklethwait, *J.*, 1912, **101**, 148) in 5% aqueous sodium hydroxide (400 c.c.) was heated to 70—80° and methyl sulphate (28 c.c.) was added in small portions to the solution which was heated for a further 15 min. A solid separated, which crystallised from alcohol to give *N*-methyl-*N*-toluene-*p*-sulphon-2-naphthalide (20·5 g.) in small needles, m. p. 72—77°. Morgan and Micklethwait (*loc. cit.*) recorded m. p. 77—78° for this compound, prepared by the action of methyl iodide on *N*-toluene-*p*-sulphon-2-naphthalide in alcoholic potassium hydroxide. The sulphonamide (20·5 g.) was warmed for 1 hr. with a mixture of concentrated sulphuric acid (25 c.c.) and glacial acetic acid (15 c.c.), cooled, and poured into water. The addition of aqueous sodium hydroxide gave a brown oil, which was extracted with benzene, and hydrogen chloride was passed into the dried ($CaCl_2$) solution. A solid separated, which on recrystallisation from alcohol saturated with hydrogen chloride, gave *N*-methyl-2-naphthylamine hydrochloride (8 g.), m. p. 176—180°. Pschorr and Karo (*Ber.*, 1906, **39**, 3141) recorded m. p. 182—183°. An ethereal solution of *o*-nitrobenzoyl chloride (from 2 g. of acid) was added slowly to *N*-methyl-2-naphthylamine hydrochloride (2 g.) dissolved in pyridine (10 c.c.) to which sodium acetate (1 g.) had been added, and the mixture was boiled under reflux for 30 min. Removal of the ether and addition of water gave a viscous red oil, which was dissolved in chloroform and washed with hydrochloric acid, water, and finally aqueous sodium carbonate. Removal of the chloroform left an oil, which was dissolved in benzene and allowed to stand. *N*-Methyl-2-nitrobenzo-2′-naphthalide (2·3 g.) separated, having m. p. 110°, identical with the compound prepared by method (*a*) above.

2-*Amino*-N-*methylbenzo*-1′-*naphthalide*.—A solution of *N*-methyl-2-nitrobenzo-1′-naphthalide (8·6 g.) in benzene (400 c.c.) and a suspension of Raney nickel (9 g.) in the same solvent were shaken with hydrogen at atmospheric pressure until the required quantity of hydrogen had been absorbed. Removal of the Raney nickel by filtration, and concentration of the filtrate, gave a solid, which on crystallisation from benzene–light petroleum (b. p. 60—80°) gave 2-*amino*-N-*methylbenzo*-1′-*naphthalide* (6·6 g.) in rectangular prisms, m. p. 144° (Found: C, 78·1; H, 5·8. $C_{18}H_{16}ON_2$ requires C, 78·3; H, 5·8%).

2-*Amino*-N-*methylbenzo*-2′-*naphthalide*.—A suspension of iron filings (50 g.) in 5% aqueous acetic acid (110 c.c.) was heated and stirred until hydrogen ceased to be evolved. The nitro-compound (11·5 g.) was added slowly and the mixture boiled for 1 hr. It was made alkaline with aqueous sodium carbonate, a little animal charcoal added, and the solution filtered whilst hot. Both filtrate and residue were repeatedly extracted with hot benzene. The combined extracts were concentrated, and crystallisation of the product from benzene–light petroleum (b. p. 60—80°) gave 2-*amino*-N-*methylbenzo*-2′-*naphthalide* (7·7 g.) in prisms, m. p. 108° (Found: C, 78·7; H, 5·9%).

Decomposition of the Diazonium Fluoroborate prepared from 2-*Amino*-N-*methylbenzo*-1′-*naphthalide*.—The amine (3·5 g.) was diazotised in concentrated hydrochloric acid (15 c.c.) and water (30 c.c.) with sodium nitrite (4 g.) in water (15 c.c.). The diazonium chloride separated as an orange solid, and was redissolved by the addition of water (250 c.c.). To the filtered solution, cooled to 0°, sodium fluoroborate (5 g.) in water (15 c.c.) was added slowly with stirring, and the yellow diazonium fluoroborate which separated was collected and dried *in vacuo* overnight. Copper powder (4 g.) was added to a suspension of the dry fluoroborate (4·6 g.) in "AnalaR" acetone (200 c.c.). There was an immediate evolution of nitrogen, and the mixture was allowed to stand for 2 hr. and then warmed on a water-bath. The mixture was filtered into water, and the residue extracted with hot acetone and boiling water. The combined aqueous and acetone solutions were extracted with chloroform, and the extract was washed with 10% aqueous sodium hydroxide. Concentration of the dried (Na_2SO_4) chloroform solution gave a brown glass-like resin (3·2 g.), which was dissolved in benzene–light petroleum (b. p. 60—80°) (1 : 1) and adsorbed on an alumina column (90 g.). Elution with the same solvent (430 c.c.) gave benzo-1-naphthalide (0·23 g.) in fluffy needles, m. p. 161°, from alcohol. There was no depression of m. p. on admixture with an authentic specimen. Further elution with the same

solvent (360 c.c.) gave a second product in rectangular plates (0·18 g.), m. p. 178—179°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 78·5, 78·9; H, 4·7, 4·8; N, 6·5%; *M*, 209). Elution with benzene–light petroleum (2 : 1) (1300 c.c.) and then with benzene–light petroleum (4 : 1) (300 c.c.) gave a third product in plates (0·4 g.), m. p. 255—256°, from benzene (Found: C, 84·0; H, 5·7; N, 6·5%; *M*, 352, 401). Further elution with benzene, benzene–ether (1 : 1), and then ether (180 c.c.) gave a yellow solid resin (1·3 g.) which could not be recrystallised. Acidification of the alkaline extract gave only a trace of tar.

Decomposition of the Diazonium Sulphate prepared from 2-*Amino*-N-*methylbenzo*-1′-*naphthalide.*—A solution of the amine (2·5 g.) in acetic acid (25 c.c.) was diazotised with nitrososulphuric acid made by the addition of sodium nitrite (3 g.) to concentrated sulphuric acid (15 c.c.) and subsequent removal of sodium hydrogen sulphate by filtration through glass wool (Hodgson and Mahadevan, *J.*, 1947, 325). The mixture was poured into ice-cold ether (400 c.c.); the diazonium sulphate separated as a yellow solid, which was washed with acetic acid–ether, and then with ether. The diazonium sulphate was decomposed under "AnalaR" acetone (200 c.c.) with copper powder (3 g.), and the products were worked up as described above. A brown resin (1·7 g.) was obtained from the chloroform extract, which was dissolved in benzene–light petroleum (3 : 1) (200 c.c.) and adsorbed on alumina (60 g.). Elution with the same solvent (510 c.c.) gave benzo-1-naphthalide (0·09 g.) in needles, m. p. 161°, from alcohol. Further elution with the same solvent (390 c.c.) gave a second product in rectangular plates (0·06 g.), m. p. 178—179°, from benzene–light petroleum, identical with the compound, m. p. 178—179°, isolated above. Elution with benzene–light petroleum (3 : 1) (200 c.c.) and then with benzene–ether (3 : 1) (180 c.c.) gave a third product in plates (0·1 g.), m. p. 255—256°, from benzene, identical with the compound, m. p. 255—256°, previously isolated. Further elution with benzene–ether mixtures and finally with ether yielded only brown tars. A trace of tar was obtained on acidification of the alkaline extract.

Decomposition of the Diazonium Fluoroborate prepared from 2-*Amino*-N-*methylbenzo*-2′-*naphthalide.*—The amine (4 g.) was diazotised in a mixture of concentrated hydrochloric acid (20 c.c.) and water (60 c.c.) with sodium nitrite (4 g.) in water (15 c.c.). Addition of sodium fluoroborate (4 g.) in water (20 c.c.) gave the solid yellow diazonium fluoroborate, which was unstable and began to redden on being washed with water. It was therefore immediately decomposed under "AnalaR" acetone (150 c.c.) with copper powder (4 g.), and the products were worked up as described above. A brown gum (3·6 g.) was obtained from the chloroform extract, which was dissolved in benzene–light petroleum (1 : 1) (200 c.c.) and adsorbed on alumina (90 g.). Elution with benzene–light petroleum (1 : 1) (200 c.c.), (2 : 1) (180 c.c.), and (3 : 1) (400 c.c.) gave a product as rectangular prisms (0·08 g.), m. p. 180—181°, from benzene (Found: C, 71·0; H, 4·8%). Elution with benzene (500 c.c.) gave N-*methyl*-3 : 4-*benzophenanthridone* (0·2 g.) in fluffy needles, m. p. 198—199°, from alcohol (Found: C, 83·0; H, 5·2. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). Further elution with benzene–ether (1 : 1) (520 c.c.) gave tars. Acidification of the alkaline extract gave a small amount of tar.

3 : 4-*Benzophenanthridine.*—(*a*) 5 : 6 : 7 : 8-Tetrahydro-3 : 4-benzophenanthridine (1·5 g.), prepared by the method of Hollingsworth and Petrow (*J.*, 1948, 1540), was heated with selenium powder (1·5 g.) for 6 hr. at 280—310°. The product was extracted with benzene, passed through an alumina column (50 g.), and eluted with benzene (400 c.c.). Removal of the benzene gave a brown oil from which crystals gradually separated. Recrystallisation of the solid from light petroleum (b. p. 60—80°) (charcoal) afforded 3 : 4-*benzophenanthridine* (0·2 g.) in needles, m. p. 110° (Found: C, 89·1; H, 4·8. $C_{17}H_{11}N$ requires C, 88·8; H, 4·9%). Kenner, Ritchie, and Wain (*J.*, 1937, 1526), who incorrectly described this compound as 3 : 4-benzacridine, recorded m. p. 106°. (*b*) 5 : 6 : 7 : 8-Tetrahydro-3 : 4-benzophenanthridine (0·5 g.) was heated with a platinum–charcoal catalyst (0·1 g.) at 280° for 2 hr. Extraction with benzene and purification as described above gave 3 : 4-benzophenanthridine (0·2 g.) in needles, m. p. 110°, identical with the specimen prepared by method (*a*).

N-*Methyl*-3 : 4-*benzophenanthridone.*—3 : 4-Benzophenanthridine (0·2 g.) and an excess of methyl iodide gave 3 : 4-benzophenanthridine methiodide (0·3 g.) as a yellow powder. To a suspension of the methiodide in a mixture of methanol (20 c.c.) and 10% aqueous sodium hydroxide (20 c.c.), an excess of alkaline potassium ferricyanide solution was added and the mixture was boiled for 20 min. and cooled. The suspended solid was collected. Extraction with alcohol left a yellow solid, m. p. 230—240°. From the alcoholic extract *N*-methyl-3 : 4-benzophenanthridone, m. p. 195—198°, was obtained, which showed no depression on admixture with the compound prepared as above from the diazonium fluoroborate prepared from 2-amino-*N*-methylbenzo-2′-naphthalide.

2′-Methoxycarbonyl-2-nitrobenzanilide.—By the procedure described above for the preparation of 2-nitrobenzo-1′-naphthalide, methyl anthranilate (13·7 g.) and *o*-nitrobenzoyl chloride (from 14 g. of acid) in the presence of pyridine (10 g.) and ether (150 c.c.) gave *2′-methoxycarbonyl-2-nitrobenzanilide* (20·5 g.) in prisms, m. p. 160°, from benzene (Found: C, 59·8; H, 4·3. $C_{15}H_{12}O_5N_2$ requires C, 60·0; H, 4·0%).

3′-Methoxycarbonyl-2-nitrobenzanilide.—By the same procedure methyl *m*-aminobenzoate (9·8 g.) and *o*-nitrobenzoyl chloride (from 10 g. of acid) gave *3′-methoxycarbonyl-2-nitrobenzanilide* (13·6 g.) in shining plates, m. p. 175—176°, from methanol (charcoal) (Found: C, 59·9; H, 4·1%).

4′-Methoxycarbonyl-2-nitrobenzanilide was similarly obtained from methyl *p*-aminobenzoate (9·5 g.) and *o*-nitrobenzoyl chloride (from 10 g. of acid) in needles (14·7 g.), m. p. 166—167°, from methanol (Found: C, 59·7; H, 3·9%).

2′-Carboxy-2-nitrobenzanilide.—(*a*) Anthranilic acid (15 g.), dissolved in 2N-aqueous sodium hydroxide (150 c.c.), and *o*-nitrobenzoyl chloride (from 18·4 g. of acid) in ether (75 c.c.) gave, by Schroeter and Eisleb's method (*Annalen*, 1909, **367**, 101), 2′-carboxy-2-nitrobenzanilide (14·5 g.) in prisms, m. p. 238—239°, from alcohol. Schroeter and Eisleb (*loc. cit.*) record m. p. 234°. (*b*) 2′-Methoxycarbonyl-2-nitrobenzanilide (28 g.) was boiled under reflux for 2 hr. with 4% aqueous sodium hydroxide (200 c.c.). Acidification gave a white solid which on crystallisation from alcohol afforded 2′-carboxy-2-nitrobenzanilide (25·2 g.) in prisms, m. p. 238—239°, identical with the product prepared by method (*a*).

3′-Carboxy-2-nitrobenzanilide.—(*a*) In similar manner *m*-aminobenzoic acid (10 g.) in 2N-aqueous sodium hydroxide (100 c.c.) and *o*-nitrobenzoyl chloride (from 12·3 g. of acid) in ether (50 c.c.) gave *3′-carboxy-2-nitrobenzanilide* (10·5 g.) in fluffy needles, m. p. 262—264°, from alcohol (Found: C, 58·4; H, 3·9. $C_{14}H_{10}O_5N_2$ requires C, 58·7; H, 3·7%). (*b*) 3′-Methoxycarbonyl-2-nitrobenzanilide (5 g.) was hydrolysed with 4% aqueous sodium hydroxide (100 c.c.) to 3′-carboxy-2-nitrobenzanilide (4·2 g.), m. p. 262—264°, identical with the specimen prepared by method (*a*).

4′-Carboxy-2-nitrobenzanilide.—(*a*) Similarly *p*-aminobenzoic acid (27 g.) and *o*-nitrobenzoyl chloride (from 33 g. of acid) gave *4′-carboxy-2-nitrobenzanilide* (25 g.) in small shining plates, m. p. 303—304°, from nitrobenzene (Found: C, 58·9; H, 3·3%). (*b*) Hydrolysis of 4′-methoxycarbonyl-2-nitrobenzanilide (20 g.) gave the same acid (16·5 g.), m. p. 303—304°.

2′-Carboxy-N-methyl-2-nitrobenzanilide.—A solution of 2′-carboxy-2-nitrobenzanilide (22 g.) in 8% aqueous sodium hydroxide (200 c.c.) was allowed to stand with methyl sulphate (18 g.) at room temperature for 30 hr. with occasional shaking. Acidification precipitated 2′-carboxy-*N*-methyl-2-nitrobenzanilide (18·5 g.), which separated from alcohol in needles, m. p. 217—218°. Schroeter and Eisleb (*loc. cit.*) recorded m. p. 216°.

3′-Carboxy-N-methyl-2-nitrobenzanilide.—Methylation of 3′-carboxy-2-nitrobenzanilide (10 g.), as described in the preceding reaction, gave *3′-carboxy-N-methyl-2-nitrobenzanilide* (5·5 g.) in yellow prisms, m. p. 176—177°, from ethyl acetate (charcoal) (Found: C, 59·7; H, 4·0. $C_{15}H_{12}O_5N_2$ requires C, 60·0; H, 4·0%).

4′-Carboxy-N-methyl-2-nitrobenzanilide.—On methylation 4′-carboxy-2-nitrobenzanilide (15 g.) gave *4′-carboxy-N-methyl-2-nitrobenzanilide* (10 g.) in small fluffy needles, m. p. 227°, from alcohol (Found: C, 60·2; H, 4·0%).

2′-Methoxycarbonyl-N-methyl-2-nitrobenzanilide.—2′-Carboxy-*N*-methyl-2-nitrobenzanilide (16 g.) in methanol (80 c.c.), saturated with dry hydrogen chloride, was boiled under reflux for 2 hr. The mixture was cooled and poured into water (400 c.c.). The solid obtained was washed with sodium carbonate solution, and recrystallised from methanol to give 2′-methoxycarbonyl-*N*-methyl-2-nitrobenzanilide (13·4 g.) in clusters of stout needles, m. p. 116—117°. Schroeter and Eisleb (*loc. cit.*) recorded m. p. 117°.

4′-Methoxycarbonyl-N-methyl-2-nitrobenzanilide, similarly prepared from the acid (15 g.), formed colourless prisms (10·2 g.), m. p. 93—94°, from methanol (charcoal) (Found: C, 61·1; H, 4·6. $C_{16}H_{14}O_5N_2$ requires C, 61·1; H, 4·5%).

2-Amino-2′-methoxycarbonyl-N-methylbenzanilide.—A solution of 2′-methoxycarbonyl-*N*-methyl-2-nitrobenzanilide (7 g.) in benzene (150 c.c.) and a suspension of Raney nickel (7 g.) in the same solvent were shaken with hydrogen at atmospheric pressure until the required quantity of hydrogen had been absorbed. The Raney nickel was removed by filtration, and the solution concentrated. Addition of light petroleum (b. p. 40—60°) gave *2-amino-2′-methoxycarbonyl-N-methylbenzanilide* (5·0 g.), which crystallised from benzene–light petroleum (b. p. 60—80°) in clusters of needles m. p. 88—89° (Found: C, 67·5; H, 5·9. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·6%).

*2-Amino-4'-methoxycarbonyl-*N*-methylbenzanilide.*—4'-Methoxycarbonyl-*N*-methyl-2-nitrobenzanilide (6·7 g.) was reduced in benzene (150 c.c.) with Raney nickel as described above. *2-Amino-4'-methoxycarbonyl-*N*-methylbenzanilide* (6·5 g.) crystallised from benzene–light petroleum (b. p. 60—80°) in clusters of needles, m. p. 103—104°, which contain half a molecule of benzene of crystallisation (Found : C, 70·4; H, 6·0. $C_{16}H_{16}O_3N_2,\frac{1}{2}C_6H_6$ requires C, 70·6; H, 5·9%). The benzene of crystallisation can be removed by a recrystallisation from methyl alcohol without any change in m. p.

*Reduction of 2'-Carboxy-*N*-methyl-2-nitrobenzanilide.*—(*a*) A solution of 2'-carboxy-*N*-methyl-2-nitrobenzanilide (1·5 g.) in an excess of aqueous ammonia was added to a boiling solution of ferrous sulphate (10 g.) in water (100 c.c.) with vigorous stirring. Ammonia (90 c.c.; *d* 0·88) was added slowly while the mixture was boiled for 20 min. The mixture was filtered hot, and acidified with acetic acid to give a clear solution, a portion of which gave a brilliant red dye when diazotised and coupled with alkaline β-naphthol. Evaporation of the solution almost to dryness gave a yellow solid, which afforded a compound regarded as *2'-carboxy-2-methylaminobenzanilide* (0·9 g.) in yellow diamond-shaped prisms, m. p. 234—235° (decomp.), from alcohol (Found : C, 66·3; H, 5·0. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2%). (*b*) 2'-Carboxy-*N*-methyl-2-nitrobenzanilide (1·5 g.) was reduced as described above. After filtration, the solution was made strongly alkaline with ammonia, and the ammoniacal solution evaporated almost to dryness. Addition of acetic acid gave a light-brown solid which on crystallisation from alcohol (charcoal) gave *2-amino-2'-carboxy-*N*-methylbenzanilide* (0·8 g.) in prisms, m. p. 182° (decomp.) (Found : C, 66·4; H, 5·3. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2%). The compound melts at 182° and then resolidifies to a yellow solid, m. p. 229—234°, which on recrystallisation from alcohol gives the product prepared by method (*a*) above (m. p. 234—235°). Schroeter and Eisleb (*loc. cit.*) prepared 2-amino-2'-carboxy-*N*-methylbenzanilide by the hydrolysis of 2-benzenesulphonamido-2'-carboxy-*N*-methylbenzanilide, and record yellowish crystals (from alcohol) which melt at 170° when heated quickly. They state incorrectly that the amine decomposes into methyldianthranilide, m. p. 259°. (*c*) 2'-Carboxy-*N*-methyl-2-nitrobenzanilide (2 g.) was reduced as described above. The filtered solution was acidified with acetic acid, and an excess of aqueous copper sulphate was added. The copper salt of the amino-acid separated in small green needles (1·5 g.), which were stirred with sodium hydroxide (0·5 g.) in water (10 c.c.); the cupric hydroxide was then removed by filtration. Addition of acetic acid to the filtrate gave 2-amino-2'-carboxy-*N*-methylbenzanilide (1 g.), m. p. 182° (decomp.), from alcohol.

*2-Amino-4'-carboxy-*N*-methylbenzanilide.*—4'-Carboxy-*N*-methyl-2-nitrobenzanilide (4·5 g.) was suspended in ethyl acetate (150 c.c.) and the minimum amount of alcohol to dissolve it was added. A suspension of Raney nickel (5 g.) in ethyl acetate was added, and the mixture was shaken with hydrogen at atmospheric pressure until the required quantity of hydrogen had been absorbed. Removal of the Raney nickel and concentration of the solution gave a yellow residue, which on recrystallisation from ethyl acetate afforded *2-amino-4'-carboxy-*N*-methylbenzanilide* (1·8 g.) in prisms, m. p. 195—196° (Found : C, 66·4; H, 5·1%).

*Decomposition of the Diazonium Sulphate prepared from 2-Amino-2'-methoxycarbonyl-*N*-methylbenzanilide.*—The amine (6·65 g.) in a mixture of concentrated sulphuric acid (6 c.c.) and water (100 c.c.) was diazotised with sodium nitrite (2 g.) in water (20 c.c.). The solution was diluted with water (280 c.c.), copper powder (7 g.) added, and the mixture stirred for 36 hr. at room temperature. Nitrogen was freely evolved. The mixture was filtered, and both filtrate and residue repeatedly extracted with hot chloroform. Removal of the chloroform from the dried (Na_2SO_4) extract left a brown gum (6·0 g.) which was extracted with benzene (200 c.c.). A buff powder (1·15 g.) remained undissolved, which on recrystallisation from a large volume of methanol (charcoal) gave small prisms (0·72 g.), m. p. 259° (decomp.) (Found : C, 63·1; H, 4·8%). The benzene solution was concentrated and adsorbed on an alumina column (35 × 2 cm.). Elution with the same solvent (200 c.c.) gave needles (0·92 g.), which on crystallisation from light petroleum (b. p. 60—80°) gave methyl *N*-benzoylanthranilate (0·76 g.) in clusters of needles, m. p. and mixed m. p. 101° (Found : C, 70·7; H, 5·1; N, 5·6. Calc. for $C_{15}H_{13}O_3N$: C, 70·6; H, 5·1; N, 5·5%). Further elution with benzene (1080 c.c.) gave yellow gums. Elution with benzene–ether (1 : 1) (220 c.c.), ether (250 c.c.), and methanol (300 c.c.) gave a yellow product (1·52 g.), which crystallised from methanol in almost colourless prisms (1·08 g.), m. p. 197° (Found : C, 69·2; H, 5·5%; *M*, 392).

*Decomposition of the Diazonium Sulphate prepared from 2-Amino-4'-methoxycarbonyl-*N*-methylbenzanilide.*—The amine (4·8 g.) was diazotised in a mixture of concentrated sulphuric acid (6 c.c.) and water (150 c.c.) with sodium nitrite (2 g.) in water (20 c.c.). The solution was diluted with water (330 c.c.), and the decomposition effected at room temperature with copper powder

(7 g.). The reaction mixture, worked up as in the previous experiment, gave a brown gum (4·56 g.), which was extracted with hot benzene (200 c.c.) and adsorbed on alumina (33 × 2 cm.). Elution with the same solvent (195 c.c.) gave a yellow gum. Further elution with benzene (475 c.c.) gave a solid (1·02 g.), which on recrystallisation from benzene gave *3-methoxycarbonyl-N-methylphenanthridone* (0·72 g.) in needles, m. p. 223—224° (Found: C, 71·8; H, 4·7. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9%). Further elution with benzene (300 c.c.) and then benzene–ether (3 : 1) (320 c.c.) gave yellow gums. Elution with methanol (405 c.c.) gave a dark red gum (1·1 g.), which crystallised from chloroform–acetone in fine needles (0·09 g.), m. p. 232—234°.

Decomposition of the Diazonium Chloride prepared from 2-Amino-2′-carboxy-N-methylbenzanilide.—A solution of the amine (2·4 g.) in concentrated hydrochloric acid (6 c.c.) and water (30 c.c.) was diazotised with sodium nitrite (2·5 g.) in water (15 c.c.). Urea (2·0 g.) was added to decompose the excess of nitrous acid, and the solution diluted with water (255 c.c.). Copper powder (3 g.) was added and the mixture stirred for 48 hr. at room temperature. The green organic copper salt which had separated was decomposed by the addition of an excess of aqueous sodium hydroxide. Cupric hydroxide and copper powder were removed from the mixture by filtration, and the residue on extraction with chloroform yielded no organic material. Acidification of the filtrate with hydrochloric acid gave a light-brown solid (1·51 g.), extraction of which with alcohol left a yellow powder (0·87 g.), m. p. 295—298° (decomp.), which was almost insoluble in all organic solvents. The solid was dissolved in aqueous sodium hydroxide, filtered, reprecipitated with acetic acid, and washed with several solvents. The product was obtained as a pale yellow powder (0·53 g.), which melted at 303—304° and immediately resolidified in long needles, which did not melt below 350° (Found: C, 69·3, 69·0; H, 4·9, 4·8%). The alcohol was removed from the extract, and the residue dissolved in light petroleum (b. p. 60—80°)–alcohol (3 : 1) and adsorbed on silica gel (10 × 2 cm.; 15 g.). Elution with the same solvent (120 c.c.) gave a brown gum (0·4 g.), which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) to give *N*-benzoylanthranilic acid (0·07 g.) in needles, m. p. and mixed m. p. 183—184° (Found: C, 69·4; H, 4·8. Calc. for $C_{14}H_{11}O_3N$: C, 69·7; H, 4·6%). Further elution gave tars.

Decomposition of the Diazonium Sulphate prepared from 2-Amino-2′-carboxy-N-methylbenzanilide.—A solution of the amine (2·4 g.) in concentrated sulphuric acid (5 c.c.) and water (30 c.c.) was diazotised with sodium nitrite (0·9 g.) in water (10 c.c.). The decomposition and purification of the products was carried out as described above for the diazonium chloride. *N*-Benzoylanthranilic acid, m. p. 183—184° (0·05 g.), was obtained. A pale yellow acidic substance (0·56 g.) was also obtained, m. p. 303—304° (decomp.), identical with the product isolated above. Hydrolysis of the compound of m. p. 197°, obtained in the decomposition of the diazonium sulphate from 2-amino-2′-methoxycarbonyl-*N*-methylbenzanilide (see above), gave a product, m. p. 303—304° (decomp.), identical with the acid, m. p. 303—304° (decomp.).

Decomposition of the Diazonium Chloride prepared from the Reduction Product of 3′-Carboxy-N-methyl-2-nitrobenzanilide.—A solution of 3′-carboxy-*N*-methyl-2-nitrobenzanilide (7 g.) in ethyl acetate and a suspension of Raney nickel (8 g.) under the same solvent were shaken with hydrogen until the theoretical quantity had been absorbed. Removal of the Raney nickel and concentration of the solution left an oil. Addition of light petroleum (b. p. 60—80°) gave a semi-solid (5 g.), which could not be recrystallised but gave a brilliant red dye on diazotisation and coupling with alkaline β-naphthol. The impure amine (5·0 g.) was diazotised in a mixture of concentrated hydrochloric acid (7 c.c.) and water (30 c.c.) with sodium nitrite (3·5 g.) in water (15 c.c.). A solid (1·0 g.) remained undissolved, which was removed by filtration and shown to be 3′-carboxy-*N*-methyl-2-nitrobenzanilide. The diazonium chloride solution was diluted with water (350 c.c.), and urea (3 g.) was added. The decomposition was effected by stirring the solution with copper powder (4 g.) for 48 hr. at room temperature. An excess of aqueous sodium hydroxide was added, and the mixture filtered. Acidification of the filtrate gave a brown solid, which was thoroughly extracted with light petroleum (b. p. 60—80°)–alcohol (4 : 1) (150 c.c.). A dark brown substance (0·43 g.) remained, which on recrystallisation from glacial acetic acid gave needles (0·21 g.) which shrank at 316° and melted at 320—322° (Found: C, 70·0, 70·1; H, 4·5, 4·5%). The light petroleum–alcohol solution was passed on to a silica gel column (25 × 2 cm.). Elution with the same solvent (150 c.c.) gave a brown solid (0·41 g.) which could not be purified. Further elution with the same solvent (230 c.c.) gave a buff solid (1·28 g.), which crystallised from glacial acetic acid to give a mixture of 2- and 4-carboxy-*N*-methylphenanthridone (0·72 g.) in needles, m. p. 260—272° (Found: C, 70·6; H, 4·4. Calc. for $C_{15}H_{11}O_3N$: C, 71·1; H, 4·4%).

Decomposition of the Diazonium Sulphate prepared from 2-Amino-4′-carboxy-N-methylbenzanilide.—A solution of the amine (2·36 g.) in concentrated sulphuric acid (5 c.c.) and water (30 c.c.) was diazotised with sodium nitrite (1 g.) in water (10 c.c.). The decomposition was carried out with copper powder (3 g.) as described above for the 2′-isomer, and the products were worked up in the same manner. An off-white solid (1·81 g.) was obtained from the acidified filtrate. Extraction of the solid with alcohol left a brown residue (0·51 g.). This *product* crystallised from nitrobenzene in needles (0·37 g.), which decomposed about 290° without melting and melted at 341—343° [Found: C, 70·7; H, 4·3; N, 5·3. $C_{30}H_{24}O_6N_2$ (dimeride) requires C, 70·9; H, 4·7; N, 5·5%]. The alcohol was removed from the filtrate and the residue dissolved in light petroleum–alcohol (4 : 1) (200 c.c.) and adsorbed on silica gel (28 × 2 cm.). Elution with light petroleum–alcohol mixtures gave no pure products.

2′ : 4′ : N-*Trimethyl-2-nitrobenzanilide.*—A solution of 2 : 4-dimethylaniline (11 g.) in pyridine (15 c.c.) and ether (150 c.c.) was condensed with *o*-nitrobenzoyl chloride (from 15 g. of acid) in ether (100 c.c.) to give 2′ : 4′-*dimethyl-2-nitrobenzanilide* (14·8 g.) in white rosettes, m. p. 163—164°, from alcohol (charcoal) (Found: C, 66·9; H, 5·2. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2%). A solution of 2′ : 4′-dimethyl-2-nitrobenzanilide (7·5 g.) in a mixture of acetone (100 c.c.) and 10% aqueous sodium hydroxide (100 c.c.) was methylated with methyl sulphate (15 g.) as described above for *N*-methyl-2-nitrobenzo-1′-naphthalide to give 2 : 4′ : N-*trimethyl-2-nitrobenzanilide* (5·5 g.) in needles, m. p. 126—127° after recrystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 68·0; H, 5·6. $C_{16}H_{16}O_3N_2$ requires C, 68·2; H, 5·6%).

2-*Amino-2′* : 4′ : N-*trimethylbenzanilide.*—A solution of the nitro-compound (4·5 g.) in benzene (150 c.c.) and a supension of Raney nickel (5 g.) in the same solvent (50 c.c.) were shaken with hydrogen until the required quantity had been absorbed. The Raney nickel was removed by filtration, and the benzene solution extracted with concentrated hydrochloric acid (50 c.c.). Evaporation of the hydrochloric acid extract to small bulk gave 2-amino-2′ : 4′ : *N*-trimethylbenzanilide hydrochloride in shining plates, m. p. 120—130° (Found: Cl, 12·1; N, 9·9. Calc. for $C_{15}H_{18}ON_2,HCl$: Cl, 12·2; N, 9·6%). Chardonnens and Würmli (*Helv. Chim. Acta*, 1950, **33**, 1344), who prepared this compound by hydrolysis of the toluene-*p*-sulphonyl derivative and treatment of the product with hydrochloric acid, recorded an indefinite m. p.

Decomposition of the Diazonium Chloride prepared from 2-Amino-2′ : 4′ : N-*trimethylbenzanilide.*—The amine hydrochloride (3·5 g.) in concentrated hydrochloric acid (5 c.c.) and water (35 c.c.) was diazotised with sodium nitrite (0·75 g.) in water (15 c.c.). Copper powder (3 g.) was added and the mixture was stirred at room temperature overnight. The mixture was filtered, and both residue and filtrate were repeatedly extracted with chloroform. The chloroform extracts were washed with 5% aqueous sodium hydroxide and dried (Na_2SO_4). Removal of the chloroform left a brown gum, which was dissolved in benzene (60 c.c.) and adsorbed on alumina (20 × 2 cm.). Elution with benzene (600 c.c.) gave 2′ : 4′-dimethylbenzanilide (0·24 g.) in shining needles (from alcohol), m. p. and mixed m. p. 193—194° (Found: C, 80·0; H, 6·7. Calc. for $C_{15}H_{15}ON$: C, 80·0; H, 6·7%). Chardonnens and Würmli (*loc. cit.*), who described this compound as 1 : 3 : 10(*N*)-trimethylphenanthridone, reported m. p. 194°. Further elution with different solvents gave gums which could not be crystallised.

2-*Amino-2′-ethyl*-N-*methyl*-4 : 5-*methylenedioxybenzanilide.*—*o*-Ethyl-*N*-methylaniline (3·5 g.), prepared from *o*-ethylformanilide (Kelly, Taylor, and Wiesner, *J.*, 1953, 2094), in ether (150 c.c.), was boiled under reflux for 2 hr. with 4 : 5-methylenedioxy-2-nitrobenzoyl chloride (from 5·5 g. of acid) in the presence of anhydrous potassium carbonate (6 g.). Removal of the ether and addition of water gave a brown solid, which was dissolved in benzene and purified on an alumina column by elution with benzene. A pale yellow solid was obtained, which on crystallisation from benzene–light petroleum (b. p. 60—80°) gave 2′-ethyl-*N*-methyl-4 : 5-methylenedioxy-2-nitrobenzanilide (5·6 g.) in pale yellow needles, m. p. 97—98°. Kelly, Taylor, and Wiesner (*loc. cit.*) recorded m. p. 106°. A solution of the nitro-compound (5·2 g.) in benzene (60 c.c.) was reduced with Raney nickel (5 g.) under benzene (100 c.c.) by shaking the mixture with hydrogen to give 2-amino-2′-ethyl-*N*-methyl-4 : 5-methylenedioxybenzanilide (4·1 g.) in shining plates, m. p. 121°, from benzene–light petroleum (b. p. 60—80°). Kelly, Taylor, and Wiesner (*loc. cit.*) recorded m. p. 121°.

2′-*Ethyl*-3 : 4-*methylenedioxybenzanilide.*—A solution of *o*-ethylaniline (3·6 g.) in ether (200 c.c.) and pyridine (10 c.c.) was condensed with 3 : 4-methylenedioxybenzoyl chloride (4·6 g.) to give 2′-*ethyl*-3 : 4-*methylenedioxybenzanilide* (5·8 g.) in shining needles, m. p. 143—144°, from alcohol–light petroleum (b. p. 60—80°) (Found: C, 71·8; H, 5·5. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%).

Decomposition of the Diazonium Sulphate prepared from 2-Amino-2′-ethyl-N-methyl-4 : 5-methylenedioxybenzanilide (cf. Kelly, Taylor, and Wiesner, *loc. cit.*).—The amine (4·1 g.) in 5% sulphuric acid (150 c.c.) was diazotised with sodium nitrite (1·5 g.) in water (10 c.c.). The clear yellow solution was heated slowly to 75° and kept at this temperature for 2 hr. during the evolution of nitrogen, and finally boiled for 2½ hr. The tarry product was extracted with chloroform and washed with 10% aqueous sodium hydroxide (200 c.c.). Removal of the chloroform from the dried (Na_2SO_4) solution left a brown gum, which was dissolved in benzene (60 c.c.) and adsorbed on alumina (30 × 2 cm.). Elution with the same solvent (520 c.c.) and crystallisation of the product from alcohol–light petroleum (b. p. 60—80°) gave 2′-ethyl-3 : 4-methylenedioxybenzanilide (0·13 g.) in shining needles, m. p. 143—144°. On admixture with the authentic specimen, prepared above, there was no depression of m. p. Further elution with benzene (600 c.c.) and then ether (1110 c.c.) gave a series of gums. Heating of the combined gums at 130—200°/0·1 mm. gave no sublimate. Elution with alcohol (60 c.c.) gave a dark red residue, which was sublimed at 130—200°/0·1 mm. A trace of sublimate, m. p. 94—96°, was obtained, which was insufficient for further investigation. It was shown that 2′-ethyl-3 : 4-methylenedioxybenzanilide sublimes unchanged at 130—150°/0·1 mm. No pure product could be isolated from the alkaline extract.

Reduction of 2′-Ethyl-3 : 4-methylenedioxybenzanilide.—2′-Ethyl-3 : 4-methylenedioxybenzanilide (1·4 g.) was boiled under reflux for 6 hr. with lithium aluminium hydride (6 g.) in anhydrous ether (300 c.c.). The pale yellow oil thus obtained formed a picrate from benzene, which on recrystallisation from the same solvent gave *2′-ethyl-3 : 4-methylenedioxybenzylaniline picrate* (1·41 g.) in yellow prisms, m. p. 124—125° (decomp.) (Found : C, 54·9; H, 4·3. $C_{16}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 54·5; H, 4·1%).

Thanks are accorded to the Delegacy of King's College for the award to D. G. T. of a Tutorial Studentship during the tenure of which this work was carried out.

King's College (University of London),
Strand, London, W.C.2. [*Received, February 27th*, 1954.]

Internuclear Cyclisation. Part X. The Preparation of 3 : 4-Benzocoumarin.*

By R. A. Heacock and D. H. Hey.

[Reprint Order No. 5169.]

Phenyl *o*-aminobenzoate has been converted into 3 : 4-benzocoumarin by a variety of methods, and the by-products formed in these reactions have been identified.

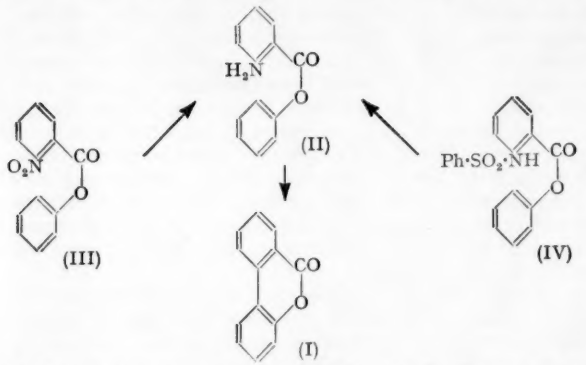
As part of work on the extension of the Pschorr phenanthrene synthesis to heterocyclic systems, the synthesis of 3 : 4-benzocoumarin (I) from phenyl *o*-aminobenzoate (II), first reported by Rule and Bretscher (*J.*, 1927, 925), has been reinvestigated, and the reaction extended to include some recently introduced methods of ring closure (Hey and Osbond, *J.*, 1949, 3164; Heacock and Hey, *J.*, 1952, 1508). Rule and Bretscher (*loc. cit.*) described the synthesis of 3 : 4-benzocoumarin in 14% yield by the diazotisation of phenyl *o*-aminobenzoate in alcoholic solution with amyl nitrite followed by decomposition of the diazonium salt with copper powder. Phenol and salicylic acid were obtained as by-products.

The present communication describes the application of five different procedures for the decomposition of the diazonium salt. Phenyl *o*-aminobenzoate (II) was prepared by (*a*) the reduction of phenyl *o*-nitrobenzoate (III), obtained from *o*-nitrobenzoyl chloride and phenol, and (*b*) the preferential hydrolysis with cold concentrated sulphuric acid for a long period of the benzenesulphonamido-group in phenyl *o*-benzenesulphonamidobenzoate (IV), prepared from benzenesulphonylanthraniloyl chloride and phenol (cf. Schroeter and Eisleb, *Annalen*, 1909, **367**, 101).

The yields of 3 : 4-benzocoumarin and the nature of the by-products formed in these reactions are shown in the Table. The major by-product was phenyl benzoate produced by deamination. Deamination in place of ring closure has been previously observed in

* Part IX, preceding paper.

similar reactions (Hey and Mulley, *J.*, 1952, 2276). Other by-products obtained included diphenyl diphenate, and salicylic and benzoic acids produced by the fortuitous hydrolysis of the ester linkage. The maximum yield of 3 : 4-benzocoumarin was obtained by decomposition of an aqueous solution of the diazonium sulphate with copper powder. No 3 : 4-



benzocoumarin was obtained on thermal decomposition of the diazonium fluoroborate in boiling light petroleum, which gave the normal replacement reaction with the formation of phenyl *o*-fluorobenzoate (cf. Balz and Schiemann, *Ber.*, 1927, **60**, 1186).

Ring-closure experiments with phenyl o-*aminobenzoate.*

Experimental conditions	Yield (%) of 3 : 4-benzocoumarin	By-products
(*a*) Action of heat on aq. diazonium sulphate	6	Salicylic acid (22%)
(*b*) Action of Cu on aq. diazonium sulphate	19·2	—
(*c*) Addition of aq. Na_2CO_3 and Cu to aq. diazonium sulphate	9	Phenyl benzoate (14%) Benzoic acid (20·5%)
(*d*) Action of Cu on solid diazonium fluoroborate in acetone	6·3	Phenyl benzoate (34·8%) Diphenyl diphenate (22·5%)
(*e*) Diazonium fluoroborate in boiling light petroleum (b. p. 80—100°)	—	Phenyl *o*-fluorobenzoate (31%)
* (*f*) Action of Cu on diazonium chloride in alcohol	14	Phenol Salicylic acid

* Rule and Bretscher (*loc. cit.*).

Authentic specimens of the hitherto unknown esters, diphenyl diphenate and phenyl *o*-fluorobenzoate, have been prepared from the acid chlorides and phenol in pyridine.

Experimental

Phenyl o-*Nitrobenzoate.*—An ethereal solution of *o*-nitrobenzoyl chloride (from 16·7 g. of acid) was added slowly to a solution of phenol (9·4 g.) in pyridine (60 c.c.). The ether was evaporated and the clear pyridine solution was boiled for a few minutes, cooled, and poured into water. A red solid separated, which on recrystallisation from aqueous alcohol (charcoal) afforded *phenyl* o-*nitrobenzoate* (12 g.) in pale yellow prisms, m. p. 52—53° (Found: C, 64·4; H, 3·8. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7%). Cahn (*J.*, 1932, 1400), who recorded no analyses, reported m. p. 42—43°, b. p. 164—165°/21 mm.

Phenyl o-*Benzenesulphonamidobenzoate.*—Benzenesulphonylanthraniloyl chloride (7 g.) and phenol (2·35 g.) were boiled under reflux in dry benzene (100 c.c.) for 21 hr. Removal of the solvent by distillation left a white solid, from which *phenyl* o-*benzenesulphonamidobenzoate* (7·5 g.) was obtained in colourless needles, m. p. 103—105°, on recrystallisation from methanol (Found: C, 64·3; H, 4·2. $C_{19}H_{15}O_4NS$ requires C, 64·6; H, 4·3%).

Phenyl o-*Aminobenzoate.*—(*a*) A solution of the nitro-ester (9·5 g.) in alcohol (200 c.c.) and a suspension of Raney nickel (10 g.) in the same solvent were shaken with hydrogen at atmospheric pressure until the required quantity of hydrogen had been absorbed. The suspension was filtered and the filtrate concentrated under reduced pressure. The base was obtained as a brown oil, which was dissolved in benzene and adsorbed on an alumina column (10 × 2 cm.). Elution of the column with the same solvent, followed by concentration of the eluant, afforded pure

phenyl *o*-aminobenzoate (4 g.) in colourless needles, m. p. 72—73°. Schmidt (*J. pr. Chem.*, 1887, **36**, 372), who prepared this compound by the action of isatoic acid on phenol, recorded m. p. 70°. Cahn (*loc. cit.*) gave m. p. 71°.

(*b*) A suspension of iron filings (80 g.) in 5% acetic acid (100 c.c.) was heated on a steam-bath, with stirring, until no more hydrogen was evolved. The nitro-ester (20 g.) was added slowly and the mixture stirred on a steam-bath for 1 hr. The solution was neutralised with aqueous sodium carbonate, and charcoal added to assist filtration. After filtration, both residue and filtrate were repeatedly extracted with hot benzene. The combined benzene extracts were concentrated to give the crude base as a brown oil, which was purified chromatographically as described under (*a*). Pure phenyl *o*-aminobenzoate (10 g.) was obtained in colourless needles, m. p. 72°.

(*c*) A solution of phenyl *o*-benzenesulphonamidobenzoate (7 g.) in concentrated sulphuric acid (30 c.c.) was set aside at room temperature for 5 days, after which it was poured into a mixture of ice and aqueous ammonia. A solid separated, which on recrystallisation from benzene–light petroleum (b. p. 80—100°) gave phenyl *o*-aminobenzoate (2·7 g.) in colourless needles, m. p. 72°.

Preparation of 3 : 4-*Benzocoumarin.*—(*a*) Phenyl *o*-aminobenzoate (2·6 g.) in concentrated sulphuric acid (10 c.c.) and water (100 c.c.) was diazotised at 0° with a solution of sodium nitrite (1 g.) in water (10 c.c.). After being stirred for 1 hr. at 0° the filtered pale yellow-green solution was heated on a steam-bath for 1 hour. The product was extracted with chloroform, and the chloroform solution was washed with dilute aqueous sodium hydroxide. Evaporation of the dried (Na_2SO_4) extract afforded a dark red oil (0·5 g.), which was dissolved in benzene–light petroleum (b.p. 60—80°) (3 : 1) and adsorbed on an alumina column (20 × 2 cm.). When the column was washed with benzene–light petroleum (b. p. 60—80°) (700 c.c.) and benzene (1000 c.c.) a pale yellow waxy solid was obtained, which on recrystallisation from light petroleum (b. p. 80—100°) gave 3 : 4-benzocoumarin (0·15 g.) in colourless needles, m. p. 92·5°. Rule and Bretscher (*loc. cit.*) recorded m. p. 93—94° for this compound. Further washing of the column with benzene, benzene–ether, and methanol gave a series of tars. Acidification of the sodium hydroxide washings and extraction with chloroform gave a black solid (1·78 g.), which was adsorbed from benzene on alumina (20 × 2 cm.). Elution of the column with the same solvent (1000 c.c.) gave salicylic acid (0·56 g.) in needles, m. p. and mixed m. p. 158°, from benzene–light petroleum (b. p. 80—100°).

(*b*) Phenyl *o*-aminobenzoate (2·9 g.) was diazotised as described above in concentrated sulphuric acid (10 c.c.) and water (200 c.c.) with sodium nitrite (1 g.) in water (10 c.c.). To the filtered solution copper powder * (3 g.) was slowly added, and nitrogen was evolved in the cold. The solution was stirred at room temperature overnight, the diazonium salt completely decomposing. The resulting suspension was filtered, and both filtrate and residue were repeatedly extracted with hot chloroform. Concentration of the dried (Na_2SO_4) extract yielded a brown tar (2·25 g.), which was adsorbed from benzene–light petroleum (b. p. 60—80°) on alumina (20 × 2 cm.). When the column was washed with benzene–light petroleum (b. p. 60—80°) (2 : 1) (1300 c.c.) and benzene (1700 c.c.) a light-coloured solid was obtained, which on recrystallisation from benzene–light petroleum (b. p. 80—100°) gave 3 : 4-benzocoumarin (0·51 g.) in colourless needles, m. p. 91—92°. Further washing of the column with benzene–chloroform (1 : 1) (500 c.c.) afforded only a trace of a brown solid. The brown solid obtained from concentration of the final washings (methanol, 500 c.c.; acetic acid, 500 c.c.) was dissolved, as far as possible, in benzene, and adsorbed on a silica gel column (20 × 2 cm.), but elution with benzene (700 c.c.) afforded only a trace of a brown unidentifiable solid.

(*c*) Phenyl *o*-aminobenzoate (2·3 g.) was diazotised, as described above, in concentrated sulphuric acid (10 c.c.) and water (100 c.c.) with sodium nitrite (0·7 g.) in water (10 c.c.). The filtered solution was decomposed by the addition of excess of aqueous sodium carbonate and copper powder (3 g.). Nitrogen was evolved in the cold, and the suspension was stirred at room temperature for 24 hr. The mixture was filtered and both filtrate and residue were extracted with chloroform. Concentration of the dried (Na_2SO_4) chloroform extract afforded a dark brown tar (1·4 g.), which was adsorbed from benzene–light petroleum (b. p. 60—80°) (4 : 1) on alumina (20 × 2 cm.). When the column was washed with benzene–light petroleum (b. p. 60—80°) (4 : 1) (300 c.c.) a yellow solid was obtained, which on recrystallisation from light petroleum (b. p. 40—60°) gave phenyl benzoate (0·3 g.) in colourless prisms, m. p. 67—68°,

* In all the reactions described in this paper the copper powder was prepared by precipitation from aqueous copper sulphate with zinc dust.

undepressed on admixture with an authentic specimen. Further washing of the column with the same solvent (1300 c.c.) gave an off-white solid, which on recrystallisation from light petroleum (b. p. 60—80°) gave 3 : 4-benzocoumarin (0·18 g.) in colourless needles, m. p. 89—90°. Final elution of the column with benzene, benzene–chloroform, and chloroform gave a series of brown tars. Acidification of the original alkaline solution and extraction with chloroform gave a dark red crystalline solid, contaminated with some tar. The product was dissolved in a mixture of benzene and light petroleum (b. p. 60—80°) (2 : 1) and adsorbed on a silica gel column (20 × 2 cm.). Washing with benzene (1500 c.c.) gave colourless crystals, m. p. 105—107°, which on recrystallisation from water gave benzoic acid (0·27 g.) in needles, m. p. and mixed m. p. 120—121°.

(*d*) A suspension of phenyl *o*-aminobenzoate (5 g.) in concentrated hydrochloric acid (20 c.c.) and water (40 c.c.) was diazotised at 0° with sodium nitrite (2 g.) in water (10 c.c.). The solution was diluted with water (40 c.c.) to keep the diazonium chloride in solution. After being stirred for 1 hr. at 0—5° the solution was filtered and sodium fluoroborate (10 g.) in water (20 c.c.) was added, with stirring, at 0°. The diazonium fluoroborate (6·9 g.) was collected and dried *in vacuo*. The fluoroborate (4·9 g.) was suspended in " AnalaR " acetone (50 c.c.) to which copper powder (3·5 g.) was added. Nitrogen was freely evolved in the cold, and the reaction was complete in 1 hr. The product was filtered into an excess of cold water. The residue was repeatedly extracted with hot acetone and boiling water, and the combined aqueous-acetone solution extracted with chloroform. On concentration, the dried (Na_2SO_4) chloroform solution gave a light brown gum (3·28 g.), which was adsorbed from benzene–light petroleum (b. p. 60—80°) (2 : 1) on alumina (20 × 2 cm.). Elution of the column with this solvent (150 c.c.) gave a pale yellow waxy solid, m. p. 50—60°, which on recrystallisation from light petroleum (b. p. 40—60°) gave phenyl benzoate (0·85 g.) in prisms, m. p. and mixed m. p. 66°. Further washing of the column with the same solvent (200 c.c.) gave a yellow solid, m. p. 62—75°, which on repeated crystallisation from light petroleum (b. p. 80—100°) gave colourless prisms, m. p. 80—81° (0·68 g.). A mixed m. p. with an authentic specimen of diphenyl diphenate (m. p. 83°) showed no depression. Continued washing of the column with this solvent (700 c.c.), with benzene–light petroleum (b. p. 60—80°) (4 : 1) (400 c.c.), and with benzene (400 c.c.), gave a light brown solid, which on recrystallisation from light petroleum (b. p. 40—60°) afforded 3 : 4-benzocoumarin (0·2 g.) in colourless needles, m. p. 91—92°. Washing of the column with benzene–chloroform (1 : 1) (700 c.c.) and chloroform (200 c.c.) gave a brown solid, which on recrystallisation from benzene–light petroleum (b. p. 80—100°) gave buff-coloured needles, m. p. 182° (Found : C, 77·6; H, 5·4%; *M*, 227). Final elution of the column with methanol (1000 c.c.) and glacial acetic acid (500 c.c.) afforded a brown glass, which was dissolved, as far as possible, in benzene and adsorbed on a silica gel column (20 × 2 cm.). Washing of the column with benzene (400 c.c.) gave only a minute quantity of a buff-coloured solid.

(*e*) The diazonium fluoroborate (2·0 g.), prepared as described above, was suspended in sodium-dried light petroleum (b. p. 80—100°), and the suspension was boiled under reflux for 44 hr. A large amount of dark insoluble material was produced, from which the pale yellow solution was decanted. The residue was extracted with benzene and the benzene extract and light petroleum solution were combined and concentrated (charcoal) to give phenyl *o*-fluorobenzoate (0·43 g.) in pale yellow prisms, m. p. and mixed m. p. 66—68°.

Diphenyl Diphenate.—Diphenoyl dichloride, prepared from diphenic acid (10 g.) by the method of Bell and Robinson (*J.*, 1927, 1698), was added to a solution of phenol (10 g.) in pyridine (50 c.c.). After being kept at room temperature for 2 days, the solution was poured into water. Crystallisation of the solid which separated from aqueous methanol (charcoal) and then from benzene–light petroleum (b. p. 80—100°) gave *diphenyl diphenate* (12·2 g.) in prisms, m. p. 83° (Found : C, 79·6; H, 4·9. $C_{26}H_{18}O_4$ requires C, 79·2; H, 4·6%).

Phenyl o-*Fluorobenzoate.*—*o*-Fluorobenzoic acid (2·0 g.), prepared by Slothouwer's method (*Rec. Trav. chim.*, 1914, **33**, 324), was boiled under reflux with thionyl chloride (20 c.c.) for 24 hr. After removal of the excess of thionyl chloride *in vacuo*, a solution of phenol (1·5 g.) in pyridine (10 c.c.) was added. After being heated on a water-bath for 30 min., the solution was poured into water and the resulting brown oil extracted with benzene and adsorbed on an alumina column (10 × 2 cm.). Washing of the column with benzene (1000 c.c.) afforded a yellow solid which, on recrystallisation from light petroleum (b. p. 40—60°), gave *phenyl* o-*fluorobenzoate* (1·3 g.) in pale yellow prisms, m. p. 70—71° (Found : C, 72·5; H, 4·4. $C_{13}H_9O_2F$ requires C, 72·2; H, 4·2%).

KING'S COLLEGE, UNIVERSITY OF LONDON,
STRAND, LONDON, W.C.2.

[*Received, February 27th*, 1954.]

The Quenching of the Fluorescence of Anthracene Gas.

By W. S. METCALF.

[Reprint Order No. 5106.]

The rates of reaction of various substances with excited anthracene molecules increase with falling temperature as would be expected if quenching collisions were increased in number by van der Waals attractive forces.

THE quenching of the fluorescence of anthracene gas by oxygen, sulphur dioxide, hydrogen iodide, and methyl, ethyl, and pentyl iodides can be described by the scheme :

$$A + h\nu \longrightarrow A^* \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \textit{Absorption}$$

$$A^* \xrightarrow{k} A + h\nu' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \textit{Fluorescence}$$

$$A^* + Q \xrightarrow{k_Q} \text{unknown products} \quad . \quad . \quad . \quad . \quad \textit{Quenching}$$

which leads to the Stern–Volmer equation : $(f_0/f - 1)/[Q] = k_t/k_Q = k$, where f_0 and f are the fluorescence intensities without and with the quencher present at a concentration [Q] moles/l. The quenching constants observed at 200° and 300° at an anthracene pressure of 1·2 mm. in hydrogen at 1 atm. pressure given in the Table were obtained over a range of quencher concentration up to the quoted value at which $f_0/f \sim 2$ from zero. In no case did k, the quenching constant, vary significantly with quencher concentration. Determinations were retained if the values of f_0 found before and after the measurement of f were consistent. Temperature coefficients, measured at the best quencher concentrations for accuracy in separate experiments in which only the temperature was altered, are significant to the number of figures given. They cannot be so accurately deduced from the quenching constants given which include measurements throughout the range of concentration quoted.

Quencher	Concn. moles/l.	Quenching constant, k 200°	300°	k_{200}/k_{300}	E
SO_2	0·0005	2180 ± 60(9) *	2210 ± 14(2)	1·020	630
O_2	0·001	932 ± 3(4)	917 ± 4(2)	1·013	590
HI	0·002	291 ± 10(8)	—	—	—
MeI	0·012	77·4 ± 2(7)	59 ± 0(2)	1·30	1940
EtI	0·012	104 ± 3(9)	79 ± 3(7)	1·29	1900
$C_5H_{11}I$	0·007	182 ± 10(4)	139 ± 2(3)	1·28	1860
$C_6H_5NH_2$	0·009	90 ± 6(7)	47 ± (1)	1·9	4000

* Values quoted are the unweighted mean and standard deviation. The figure in parentheses are the number of determinations made.

Self-quenching of anthracene reduces the quenching constants as the anthracene pressure increases. Preliminary measurements over a range of anthracene pressures showed that the k values extrapolated to zero anthracene concentration differed by about 2% from those quoted. Recent direct measurements of the self-quenching of anthracene (Bowen and Stevens, personal communication) show that the k values in the Table are 3% low on this account.

In the last column are given the values of E required to fit the equation $k = AT^{1/2}e^{+E/RT}$ to the observed temperature coefficients. E, the work done (cal./mole) by the forces of attraction as the excited anthracene and quencher molecules approach the point where energy degradation occurs, requires a value of 516 cal./mole to produce a zero temperature coefficient between 200° and 300°, because of the term $T^{1/2}$ in the equation above. The small but definite negative temperature coefficients of quenching by oxygen and by sulphur dioxide indicate the slightly higher attractive energies shown. The more complex quenchers show a very marked decrease in efficiency with rising temperature, with a correspondingly high negative value of the " activation energy." k_t is assumed to be independent of temperature.

The values of E may be compared with the following values calculated from the temperature coefficient of the viscosity of various gases (cf. " Handbook of Chemistry and Physics,"

Chemical Rubber Publ. Co., Cleveland, 1944) by the equation $\eta = \eta_0 T^{1/2} e^{-E/RT}$ (Loeb, "The Kinetic Theory of Gases," McGraw-Hill, New York, 1934, p. 225), in which E is the work done (cal./mole) by the attractive forces as the molecules approach the collision distance: O_2, 170; HI, 354; SO_2, 380; C_6H_6, 470; $Me{\cdot}CO_2Bu^i$, 1250 cals./mole. These values increase with molecular weight and boiling point. It seems therefore that the negative temperature coefficients of quenching are no greater than can be attributed to the attractive forces expected between anthracene and quencher molecules.

Increase in the length of the alkyl group of alkyl iodides enhances the quenching without increasing the negative temperature coefficient. This behaviour is doubly curious in that the larger alkyl groups would be expected to decrease the quenching by obstructing the iodine atom, which effect might be somewhat offset by an increased van der Waals attraction and a correspondingly larger negative temperature coefficient. As this is not so, the enhancement appears to be due to the increase in the collision diameter of the quencher which behaves as a whole rather than as an active iodine atom with an inactive "tail." By contrast, quenching by hydrogen iodide is high, as is expected if the unhindered approach of the iodine atom to the excited anthracene molecule is the essential part of the quenching process.

Experimental.

The photometer has already been described (*J.*, 1954, 976).

Hydrogen, freed from oxygen, was saturated with quencher in three successive bubblers of thin glass in a temperature-controlled water- or oil-bath. In the cases of oxygen, sulphur dioxide, and hydrogen iodide, mixtures with hydrogen were stored in reservoirs. The mixture, kept hot electrically to prevent condensation, passed through a series of eight bulbs containing pure anthracene heated externally by the condensing vapour of anisole (b. p. 155°). The mixed gases entered a Pyrex tube (4″ × 1″) surrounded by an aluminium block regulated at 200° or 300° as required. Double windows at right angles admitted the exciting light (3650 Å) to the tube and passed the fluorescence to the photocell. The reference photocell observed a similar tube, in the same aluminium block, containing anthracene maintained at a steady pressure by a side arm in a second aluminium block whose temperature was set for maximum fluorescence. For the determination of f_0, the hydrogen by-passed the quencher saturator.

The flow-rate and the total pressure were controlled. The fluorescence intensity and the quenching constant were independent of flow-rate over a considerable range, and about two min. were normally required to reach a steady value. In no case did the partial pressure of carrier gas affect the fluorescence intensity or the quenching constant. With sulphur dioxide the same constant is found when either hydrogen or nitrogen is used as carrier gas. Values for sulphur dioxide obtained in the absence of carrier gas are less accurate because flow rates are difficult to control at low pressures, but they do not differ significantly from the results quoted. The discrepancy with the value of 1000 given by Bowen and Metcalf (*Proc. Roy. Soc.*, 1951, *A*, **206**, 437) obtained in a static apparatus has not been resolved.

Oxygen and sulphur dioxide were obtained from cylinders and were not purified further. Hydrogen iodide was prepared by combination of the elements over hot platinum, and fractionated in liquid air traps. As hydrogen iodide attacks mercury its pressure was measured by a spoon gauge.

Methyl iodide, ethyl iodide, and aniline were fractionally distilled (20 plates). Their vapour pressures were measured in an isoteniscope immersed in the bath used for the saturators, thus avoiding thermometric errors. When the stem correction was applied the vapour pressures agreed with those quoted by Timmermans ("The Physico-Chemical Constants of Pure Organic Compounds," Elsevier, 1950). The vapour pressure of pentyl iodide (d_4^{20}, 1·5170) similarly purified was as follows:

p_{mm}	20	30	40	60	80	100	150
$T°$ (corr.)	53·7	62·5	68·9	78·6	85·6	91·5	102·7
p_{mm}	200	300	400	500	600	700	760
$T°$ (corr.)	111·4	123·8	133·3	141·0	147·4	153·0	156·0

Victoria University College,
Wellington, New Zealand.

[*Received, February 19th*, 1954.]

The Promotion of Raney Nickel Catalysts.

By Robert B. Blance and David T. Gibson.

[Reprint Order No. 5206.]

Delépine has shown that, in the hydrogenation of ketones, Raney nickel is promoted by treatment with chloroplatinic acid followed by sodium hydroxide. Lieber has shown that treatment with triethylamine and chloroplatinic acid is also effective. We find that a combination of the two techniques is better than either, and that lithium hydroxide can, with advantage, replace sodium hydroxide.

In addition to successive improvements (Adkins, *J. Amer. Chem. Soc.*, 1948, **70**, 695) in the preparation of Raney nickel catalysts it has been shown that for many reductions the catalyst is promoted by treatment with sodium hydroxide, chloroplatinic acid, triethylamine, etc. Delépine and Horeau (*Bull. Soc. chim.*, 1937, **4**, 31) found that Raney nickel platinised with chloroplatinic acid solution was substantially promoted for reduction of the carbonyl group, but not of double bonds, by treatment with a little aqueous sodium hydroxide. Lieber and Smith (*J. Amer. Chem. Soc.*, 1936, **58**, 1417) added to Raney nickel triethylamine followed by chloroplatinic acid solution. The sparingly soluble triethylamine chloroplatinate deposited platinum on the catalyst, so that the platinising is probably more uniform than by direct addition of chloroplatinic acid to the nickel suspension, for then the first particles to encounter the solution would be overplatinised and the remainder unplatinised. The possibility of uneven platinising is confirmed by Delépine and Horeau's observation (*loc. cit.*) that whereas Raney nickel dissolves completely in dilute acid, platinised Raney nickel always leaves a small nickel-containing residue. Heilman, Dubois, and Beregi (*Compt. rend.*, 1946, **223**, 737), using Raney nickel W1, reported the superiority

Table 1. *Time (minutes) for hydrogenation of ketones Promotor for the Raney nickel catalyst.*

Ketone	None	NaOH	Et_3N	Pt + NaOH	Et_3N + Pt	Et_3N + Pt + NaOH
			Reaction at 1 atm.			
Dimethyl	39	24	31	21	25	16
Ethyl methyl	52	38	47	27	47	19
Methyl *n*-propyl	76	36	64	30	83	21
Methyl *n*-pentyl	77	57	83	33	93	25
*iso*Butyl methyl	78	53	—	35	126	27
Diethyl	80	—	—	37	221	27
n-Butyl ethyl	82	—	—	38	265	34
Di*iso*propyl	*i*	—	—	253	*x*	*i*
*cyclo*Hexanone	40	40	—	21	37	17
4-Methyl*cyclo*hexanone	60	45	—	23	36	20
2-Methyl*cyclo*hexanone	88	65	—	45	161	32
2 : 2-Dimethyl*cyclo*hexanone	93	70	—	49	167	32
2 : 2 : 6-Trimethyl*cyclo*hexanone	472	—	—	264	*i*	200
2 : 2 : 6 : 6-Tetramethyl*cyclo*hexanone	*i*	—	—	1600	—	1600
Camphor	580	—	—	329	—	153
Acetophenone	57	30	38	19	15	14
Propiophenone	90	55	65	34	24	24
Benzophenone	70	40	39	38	34	16
			Reaction at 3 atm.			
3-Methyl*cyclo*hexanone	24	—	—	11·5	15	9
4-Methyl*cyclo*hexanone	24	—	—	11	15	9
Fenchone	—	—	—	*i*	—	720

i = incomplete reaction; *x* = no absorption of hydrogen.

of Delépine's method "sur un grand nombre d'autres composées à fonction carbonyle." We compared the two methods for the reduction of ketones by using Raney nickel W4, and we found that for aliphatic and alicyclic ketones Delépine's method was superior, but that with some aromatic ketones, Lieber's method was slightly better. Further, we found that in all

cases a combination of the two techniques, *i.e.*, platinising the catalyst by using triethylamine (Lieber), followed by addition of sodium hydroxide (Delépine), was superior to either. The rates of hydrogenation at 1 and at 3 atmospheres pressure were invariably increased, usually by as much as 20%. Table 1 shows that while Lieber's catalyst is fairly efficient for acetone and *cyclo*hexanone, its performance is considerably poorer for higher ketones. Sodium hydroxide, however, extends the range of efficiency and also retards the ageing of the catalyst.

The promoted catalyst (0·5 g.), ethanol (20 ml.), the ketone (10 mmoles), and 10N-sodium hydroxide (1—2 mmoles) were shaken with hydrogen at 200 double strokes per minute. The best results were obtained with a catalyst promoted by adding triethylamine (3·3 mmoles), chloroplatinic acid (0·04 mmoles) and finally 10N-sodium hydroxide (1·2 mmoles) to a rapidly stirred suspension of Raney nickel catalyst (0·5 g.). The catalyst was then washed three times with distilled water and three times with alcohol. Ketones and solvent were left overnight in contact with Raney nickel to remove poisons and were filtered and redistilled. The Raney nickel catalyst was prepared from Murex 50% nickel–aluminium Alloy (80 to dust) by Adkin's and Pavlic's method (*J. Amer. Chem. Soc.*, 1946, **68**, 1471) for Raney nickel catalyst W4.

Since Patterson and Degering (*J. Amer. Chem. Soc.*, 1951, **73**, 611) have reported poisoning of Raney nickel by chloride ion, we avoided the use of chloroplatinic acid by preparing the catalyst from a specially made aluminium–nickel alloy containing 2% of platinum. Table 2 shows that this catalyst is not only better than the unpromoted catalyst, but is at least as efficient and much easier to use than our promoted catalyst for the more difficult hydrogenations.

TABLE 2. *Times of hydrogenation of ketones with Raney nickel catalysts perpared from* Ni–Al *containing* 2% *of platinum.*

	Un-promoted	Promoted by NaOH		Un-promoted	Promoted by NaOH
Dimethyl ketone	41	23	2 : 2′ : 6-Trimethyl*cyclo*-hexanone	352	159
*cyclo*Hexanone	40	27	(+)-Camphor	273	155
2-Methyl*cyclo*hexanone ...	54	28			

Since the completion of these experiments, Cornubert and Phélisse (*Bull. Soc. chim.*, 1952, **19**, 403) have confirmed that Raney nickel is poisoned by chloride ion, but showed that at a chlorine : catalyst ratio of 1 : 100 the effect is scarcely detectable. As we had used 1 mole of chloroplatinic acid per 500 moles of catalyst, it is evident that even if *none* of the liberated chloride had been removed in the subsequent washing, its effect on the catalyst would have been negligible.

The promoting effect of sodium hydroxide has been ascribed by Dupont and Piganiol (*ibid.*, 1939, **6**, 322) to localised adsorption of ketone on areas containing adsorbed sodium ions. Assuming that the hydrogen is adsorbed on areas free from sodium, they postulated that reaction takes place at the boundaries. While their view may account for the existence of an optimum amount of sodium hydroxide (which we found to be 0·4 mmole per g. of catalyst)(cf. Cornubert and Kaziz, *ibid.*, 1952, **19**, 410) it suggests that sodium hydroxide should, in the absence of an acceptor, diminish the amount of hydrogen taken up by Raney nickel. Actually, we found that addition of sodium hydroxide caused adsorption of an additional 5 ml. of hydrogen per g. of nickel. Our results are more in harmony with Bremner and Keey's views (*J.*, 1947, 1079) that the catalyst may be regarded as an electron donor or acceptor, and that addition of electropositive ions to it will tend to increase its electron-donor characteristics, so that alcohol will tend to be desorbed. The increased rate of hydrogenation of carbonyl compounds following the addition of alkali may therefore be due to an increase in the catalyst area made available by the more rapid desorption of the alcohol resulting from the reduction.

In a study of the catalytic reduction of ethylenes in solution in various alcohols, Schmidt (*Z. physikal. Chem.*, 1936, *A*, **176**, 254) considered that a measure of the relative affinities of the solvent and of the ethylene for the catalyst surface was given by the ratio of their heats of vaporisation. Thus, where the ratio was large, reaction was slow because of a preferential adsorption of solvent molecules on the surface, tending to prevent access of ethylene.

A similar correspondence was noted in the present work; the activity of the catalyst was

enhanced by the presence of sodium hydroxide in cases where the heat of vaporisation of the product is substantially greater than that of the original ketone. This is confirmed by the results of Samuelson, Garik, and Smith (*J. Amer Chem. Soc.*, 1950, **72**, 3872) for the majority of simple nitro-compounds examined. On the other hand the ratio of the heats of vaporisation of *cyclo*hexene and *cyclo*hexane is nearly unity and addition of sodium hydroxide slightly retards reaction. Some of these results are collected in Table 3.

TABLE 3.

Substrate	Heat of vaporisation, kcal. mole^{-1}	Reduction product	Heat of vaporisation, kcal. mole^{-1}	Effect of NaOH
Acetone	7·26	2-Propanol	9·56	Promotes
Ethyl methyl ketone	7·59	2-Butanol	9·92	,,
*cyclo*Hexanone	9·50	*cyclo*Hexanol	10·70	,,
Nitrobenzene	7·94	Aniline	9·91	,,
*cyclo*Hexene	7·28	*cyclo*Hexane	7·34	Retards

Cornubert and Phélisse (*loc. cit.*) demonstrated elegantly the selective character of promotion by sodium hydroxide by showing that in its absence unsaturated ketones were rapidly and sharply converted into saturated ketones, and that thereafter the reduction could be continued to give the saturated alcohol by adding sodium hydroxide.

The similarity between the ionic radii of lithium and of nickel suggested that if promotion is due to adsorption of sodium ions lithium hydroxide might function better. The results in Table 4 show that lithium hydroxide is about 20% better than sodium hydroxide. Optimum results are obtained by using 0·6 mmole of lithium hydroxide per g. of Raney nickel.

TABLE 4. *Times for hydrogenation of ketones with Raney nickel and alkali.*

Ketone	Un-promoted	Promoted by NaOH	Promoted by LiOH	Ketone	Un-promoted	Promoted by NaOH	Promoted by LiOH
Dimethyl	39	31	25	Methyl *n*-propyl	70	41	34
Ethyl methyl	54	35	30	*n*-Butyl methyl	81	60	42

Potassium hydroxide was a less efficient promoter than sodium hydroxide for reduction of ethyl methyl ketone (1·17 : 1) and *n*-butyl methyl ketone (1·33 : 1).

The authors thank the Mond Nickel Co. for the loan of diffusion apparatus, Messrs. Murex for making special alloys containing platinum, Messrs. Glaxo for a gift of ketones, and Mr. Steele for assistance with the lithium hydroxide experiments.

UNIVERSITY OF GLASGOW. [*Received, March 12th*, 1954.]

Conjugated Macrocycles. Part XXV. Cross-conjugated Macrocycles with Inner Great Rings of 16, 20, and 24 Atoms.*

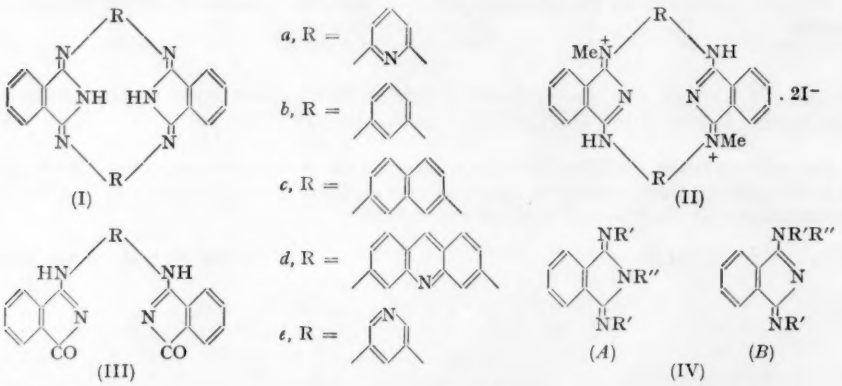
By P. F. Clark, J. A. Elvidge, and R. P. Linstead.

[Reprint Order No. 5222.]

The formation of cross-conjugated macrocycles by the condensation of 1 : 3-di-imino*iso*indoline with appropriate diamines has been further studied. Thus from *m*-phenylenediamine, 2 : 7-diaminonaphthalene, and 2 : 8-diaminoacridine, the macrocycles (I*b*, *c*, and *d*) were obtained, which have 16-, 20-, and 24-membered inner great rings. With 3 : 5-diaminopyridine the reaction yields the macrocycle (I*e*). This is a positional isomer of the macrocycle (I*a*), previously prepared from 2 : 6-diaminopyridine. Unlike (I*a*), and in keeping with their structure, the new macrocycles do not co-ordinate metals centrally, though (I*e*) forms amorphous insoluble compounds with copper and zinc acetates. These may have macromolecular extended-lattice structures.

The new macrocycles have been hydrolysed quantitatively, and their light absorptions determined. The formation of compounds with mineral acids, acetic acid, and methyl iodide has been examined. The structures of the macrocycles and their salts are discussed and compared with those of related linear compounds.

A previous paper (Elvidge and Linstead, *J.*, 1952, 5008) described the formation of a novel type of cross-conjugated macrocycle (I*a*) by the condensation of 1 : 3-di-imino*iso*indoline (IV; R′ = R″ = H) with 2 : 6-diaminopyridine. As mentioned there and elsewhere (Linstead, *J.*, 1953, 2873), the reaction was a ready one and capable of extension.



We now describe the further macrocycles (I*b*, *c*, *d*, and *e*), which we have obtained by condensing the di-imine in boiling butanol with the diamines, *m*-phenylenediamine, 2 : 7-diaminonaphthalene, 2 : 8-diaminoacridine, and 3 : 5-diaminopyridine. The yields and some characteristics of the macrocycles are given in Table 1. It is noteworthy that the naphthalene macrocycle † (I*c*), which has an inner cross-conjugated great ring of 20 atoms, is no less easily prepared than the benzene macrocycle (I*b*) and the two isomeric pyridine macrocycles (I*a*) and (I*e*), which all have 16 atoms in their inner great ring.

The related linear 3-unit compounds (III*a*—*e*) and (IV; R′ = 2-pyridyl, Ph, 2-naphthyl, and 3-pyridyl, R″ = H) have already been described (Elvidge and Linstead, *J.*, 1952, 5000; Clark, Elvidge, and Linstead, *J.*, 1953, 3593).

* Part XXIV, *J.*, 1952, 5008.

† This type of nomenclature is used in the absence of generally agreed systematic names.

The gross structure of the 2 : 6-pyridine macrocycle (I*a*) followed from its preparation, hydrolysis, and molecular formula (see *J.*, 1952, 5008). Dr. J. C. Speakman of Glasgow University examined crystals of the derived nickel complex by the *X*-ray method and obtained an electron-density projection which gave detailed confirmation of the macrocyclic structure (*Acta Cryst.*, 1953, **6**, 784; Linstead, *loc. cit.*). Interesting features of the nickel compound are (*a*) the non-coplanarity of the pyridine and *iso*indole rings with the inner great ring of the molecule, and (*b*) the bond lengths, which indicate a predominating contribution from a fully conjugated canonical form as was suggested (*J.*, 1952, 5008) on light-absorption evidence.

The new compounds now reported are given macrocyclic structures (I) by analogy with the 2 : 6-pyridine compound (I*a*). They are prepared similarly, the elementary analyses show the absence of end groups (amino or imino) which would necessarily be present in linear condensation products, and they are hydrolysed to the original diamine and phthalic acid in good yields and equivalent proportions (Table 1), which shows that equal numbers of the two units are combined alternately [as in (I)]. Determination of the molecular weights of the benzene and naphthalene macrocycles by the ebullioscopic method gave values in agreement with the 4-unit structures (I*b* and *c*). The evidence for these structures is, therefore, complete.

TABLE 1.

Macrocycle	Method of purification	Yield (%)	Form and m. p.	Mol. formula (Found)
(I*b*)	Sublimation at 340°/15 mm.	70	Long yellown needles, 380°	$C_{28}H_{18}N_6$
(I*c*)	Sublimation at 400—450°/15 mm.	70	Fine yellow needles, *ca.* 500° (decomp.)	$C_{36}H_{22}N_6$
(I*d*)	Extractive crystn. from pyridine	18	Deep yellow rods, bronze lustre, decomp. >400°	$(C_{21}H_{12}N_4)_x$*
(I*e*)	Crystn. from hot nitrobenzene	46	Minute yellow needles, 436° (decomp.)	$(C_{13}H_8N_4)_x$*
(I*a*) †	,, ,,	40	Orange-red laths, 344°	$C_{24}H_{16}N_8$

	Hydrolysis ‡		
Macrocycle	Necessary conditions	P	D
(I*b*)	1 : 1 conc. HCl–AcOH, 150°/7 hr.	1·90	1·79
(I*c*)	1 : 1 conc. HCl–AcOH, 180°/15 hr.	1·68	1·84
(I*d*)	Boiling conc. HCl	1·63	1·93
(I*e*)	Boiling 2N-HCl	1·78	1·64
(I*a*) †	Warm conc. HCl, 10 min.	Phthalimide, 1·86	1·56

* x undetermined, but presumably = 2, for steric reasons, and by analogy.
† Data from *J.*, 1952, 5008.
‡ P = yield of phthalic acid in mols.; D = yield of diamine (picrate) in mols.

Attempts similarly to determine the molecular weights of the acridine and 3 : 5-pyridine compounds failed, unfortunately, because of the very low general solubilities of these compounds. Comparison of the physical and chemical properties of these two compounds with those of the other products (I*a*, *b*, and *c*) leaves little doubt, however, that they have the analogous 4-unit macrocyclic structures (I*d* and *e*).

The new macrocycles are very stable thermally, particularly the benzene and the naphthalene compounds, (I*b* and *c*). These two are also resistant to hydrolysis by boiling concentrated hydrochloric acid. The acridine and the 3 : 5-pyridine macrocycle are more easily hydrolysed, but not so readily as the 2 : 6-pyridine macrocycle (I*a*). From that compound phthalimide was consequently obtained in good yield (*J.*, 1952, 5008), and not phthalic acid as in the present cases (Table 1). Qualitatively similar differences in the ease of hydrolysis were shown by the related linear 3-unit derivatives (IV; R′ = 2-pyridyl, Ph, and 2-naphthyl, R″ = H) (*J.*, 1953, 3593).

The macrocycles gave coloured solutions in cold concentrated sulphuric acid. As indicated in Table 2, addition of ice to the solutions produced in most cases coloured precipitates, presumably of the sulphates, from which the macrocycles were regenerated by alkali. The 2 : 6-pyridine macrocycle, however, was soluble in the diluted acid and

was hydrolysed to phthalimide in about 15 min. The 3 : 5-pyridine macrocycle was hydrolysed about half as rapidly.

Easier to prepare for analytical examination were the hydrochlorides. Under anhydrous conditions, the benzene and the naphthalene macrocycle (I*b* and *c*) formed orange-red and scarlet dihydrochlorides. Presumably, the basic centres are the two phthalic imidine residues in the molecules of these compounds. The 3 : 5-pyridine macrocycle (I*e*) formed a salmon-pink dihydrochloride when treated with dilute hydrochloric acid. This is presumably a dipyridinium dichloride. Difficulty was experienced in preparing a stoicheiometric salt from the highly insoluble acridine macrocycle (I*d*), and dark red products containing between 1 and 3 mols. of hydrogen chloride were obtained. All the hydrochlorides were very stable thermally.

TABLE 2.

Macrocycle	Colour of solution in conc. H_2SO_4	Effect of adding ice (and alkali)
(I*b*)	Yellow	Orange ppt. $\xrightarrow{\text{alkali}}$ (I*b*), 99%
(I*c*)	Orange	Scarlet ppt. $\xrightarrow{\text{alkali}}$ (I*c*), 100%
(I*d*)	Olive-green	Dark red ppt. $\xrightarrow{\text{alkali}}$ (I*d*), 98%
(I*e*)	Deep yellow	Orange ppt., changing to phthalimide (32%) in 30 min.
(I*a*)	Orange	Orange ppt., changing to phthalimide in 15 min.

The macrocycles also combined with acetic acid but the products were not stable to heat. Thus the benzene macrocycle (I*b*) formed an orange crystalline product with 3 mols. of acetic acid, from which the macrocycle was regenerated at 155°, and the acridine macrocycle (I*d*) yielded a red diacetate trihydrate, which lost acetic acid at 210°. The naphthalene macrocycle formed an orange-coloured compound (apparently non-stoicheiometric) which lost acetic acid at 180°. It seems that these products are crystal solvates rather than salts of acetic acid. The yellow product from the 3 : 5-pyridine macrocycle (I*e*), however, which contains 2 mols. of combined acetic acid, is probably a dipyridinium diacetate.

Quaternisation of the macrocycles with methyl iodide was also examined. As previously mentioned (*J.*, 1952, 5008), the 2 : 6-pyridine macrocycle (I*a*) failed to react at 100°. The 3 : 5-pyridine macrocycle (I*e*), on the other hand, easily formed a (sparingly soluble) dimethiodide. Acid hydrolysis of this and treatment of the hydrolysate with picric acid afforded in good yield 3 : 5-diamino-1-methylpyridinium picrate. Quaternisation of the macrocycle (I*e*) had therefore occurred on the pyridine-nitrogen atoms : these, being situated on the periphery of the great ring system in the molecule, are accessible to the reagent. Surprisingly, the benzene and the naphthalene macrocycles (I*b* and *c*) formed dimethiodides : these were insoluble and infusible. It seems likely in these derivatives that quaternisation has been effected on two of the four nitrogen atoms which provide the aza-links ; one of the possible bond structures is shown in formula (II).

Attempted degradation of the dimethiodides of the benzene and the naphthalene macrocycle (II*b* and *c*) by acid hydrolysis unfortunately produced intractable tars. With warm aqueous sodium hydroxide, however, the orange-red benzene macrocycle dimethiodide (II*b*) yielded a yellow solid, which was readily soluble in methanol, unlike the parent macrocycle or its salts. Crystals of the product rapidly effloresced in the air and afforded the (sparingly soluble) parent benzene macrocycle (I*b*). The new (soluble) product was not merely a methanol solvate of the macrocycle, however : it was evidently the dimethohydroxide corresponding to (II*b*). This was shown by the following results. Treatment of the product with hydrogen iodide regenerated the dimethiodide (II*b*). The benzene macrocycle hydriodide, prepared for comparison, differed in being maroon-coloured, and in giving back the macrocycle instantly with alkali. Moreover, an authentic dimethanol solvate of the benzene macrocycle was obtained by keeping the macrocycle under methanol for several days. It formed yellow needles, which did not effloresce and were only sparingly soluble in methanol.

The highly insoluble crimson naphthalene macrocycle dimethiodide (II*c*) reacted with

aqueous alkali only very slowly even at the boiling point, to regenerate the naphthalene macrocycle (Ic) (presumably *via* an unstable quaternary hydroxide).

Under the conditions previously employed, methylation of the acridine macrocycle was incomplete, and the dark product contained only 1·6 mols. of combined methyl iodide. It was hydrolysed cleanly in boiling hydrochloric acid, and an orange chloride was isolated. This has not been identified and the position of methylation of the acridine macrocycle remains uncertain.

Of the cross-conjugated macrocycles which we have so far described, only the 2 : 6-pyridine macrocycle (Ia) has a central structural arrangement akin to that in the porphyrins and azaporphins. As was expected, therefore, only this compound of the present series formed analogous complexes with one equivalent of bivalent metals (*J.*, 1952, 5008). No metal-containing derivatives could be obtained from the benzene, naphthalene, and acridine macrocycles. Incidental to the experiments, a crystal solvate of the last macrocycle was encountered, which contained 2 mols. each of formamide and water. However,

TABLE 3. *Ultra-violet light absorption characteristics of macrocycles and related linear compounds.*

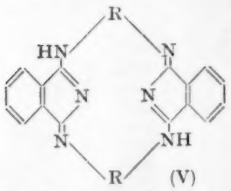
Macrocycle (I) (in H·CO·NMe$_2$)	$\lambda_{max.}$ (Å)	ε	Compound (IV) (in EtOH) †	$\lambda_{max.}$ (Å)	ε
b	2800	25,000	(i) R′ = Ph, R″ = H	2510	12,200
	3280 } 3430 }	17,100		2560	
				2640	
				3030 } 3280 }	8,900
				3480	7,700
				3650	6,500
c	2800	44,200	(ii) *B*, R′ = Ph, R″ = Me	2580	11,200
	3050	32,400	(see p. 2494)	2680	12,400
	3150	27,500		2810	
	3350	29,100		2900	
	3520	32,400		3680	14,600
	3620	31,800			
d	2800	58,900	(iii) R′ = 2-naphthyl, R″ = H	2270 } 2340 }	63,500
	3240	46,000		3260	9,100
	3360	53,100		3600	10,750
	3630	46,000			
e	2800 } 2900 }	27,800	(iv) R′ = 3-pyridyl, R″ = H	2350	29,900
	3150	19,800		2510	14,300
	3300	22,900		2660	12,500
				2800	
				2900	
				3040	
				3150	
				3530	10,700
a	2800	*	(v) R′ = 2-pyridyl, R″ = H	2310	31,300
	2900			2740	19,800
	3240			2840 ‡	18,500
	3430			3300	16,900
				3450	18,300
				3640	20,500
				3830	21,800

* The solution is too dilute for accurate intensity measurements (*J.*, 1952, 5008).
† From *J.*, 1953, 3593; 1952, 5000. ‡ Inflexion.

the 3 : 5-pyridine macrocycle (Ie) with copper and zinc acetates in dimethylformamide yielded a brown copper derivative, $C_{30}H_{28}O_7N_8Cu_2$, and a yellow zinc derivative, $C_{30}H_{28}O_7N_8Zn_2$. The empirical formulæ showed that 2 atoms of metal were combined with one macrocycle residue, together with acetate residues and water, thus: $C_{30}H_{28}O_7N_8M_2$ is made up of $C_{26}H_{16}N_8 + 2OAc + 3H_2O + 2M$. The derivatives were amorphous, insoluble, infusible, and very stable thermally. Consequently we suggest that these metal derivatives have macromolecular extended-lattice structures. Certainly they are not complexes of the normal porphyrin or azaporphin type, which indeed are not to be expected.

The light absorptions of the macrocycles (I) are given in Table 3, which includes, for comparison, the data for the related linear 3-unit compounds (IV). The spectra of the macrocycles accord with the cross-conjugated structures. They show that the macrocycles have no chromophores additional to the chromophoric systems present in the corresponding linear 3-unit compounds (IV). There can be no contribution to the structures from (conceivable) tautomers in which there is a fully conjugated great ring, in the way that is evident for the nickel derivative of the 2 : 6-pyridine macrocycle, as mentioned already.

It was concluded previously (*J.*, 1953, 3593) that the linear compounds (IV; R″ = H) were capable of tautomerism. Members of the series appeared to exist in solution either in the di-imino*iso*indoline form (IV*A*) or the aminoimino*iso*indolenine form (IV*B*), or as mixtures. A characteristic of compounds with the fixed structure (IV*B*), *e.g.* (ii) (Table 3), was absorption of light in the 3680—3790 Å region, whilst the structure (*A*) appeared not to show absorption maxima beyond about 3200 Å. It was concluded that the diphenyl derivative (i) (Table 3) was a tautomeric mixture of the two forms in solution. In the dinaphthyl compound (iii), it appeared that the *iso*indolenine form (*B*) predominated. We can add that the di-3-pyridyl compound (iv) appears to be a mixture, whilst the di-2-pyridyl isomer (v) probably exists entirely in the form (*B*), in ethanol.


(V)

By making comparisons, we can tentatively assign fine structures to the macrocycles. The benzene and the two pyridine macrocycles do not absorb light at such long wave-lengths as the corresponding linear compounds. We suggest therefore (from Table 3) that these three macrocycles (in dimethylformamide) correspond predominately to the type (*A*) structure, and are probably best represented by the formulæ (I*b*, *e*, and *a*). In the naphthalene and the acridine macrocycle there appears to be a greater contribution from form (*B*) structures, so that the alternative representations (V*c* and *d*) seem more appropriate.

The hydrochlorides (and methiodides) of the benzene, naphthalene, and acridine macrocycles are more deeply coloured than the parent compounds. Because of their insolubility it was not possible to determine by ultra-violet absorption methods whether the salts had structures analogous in type to that proposed for the hydrochloride of diphenyliminoisoindoline (*J.*, 1953, 3593). This hydrochloride in acetic acid showed an absorption maximum at 3980 Å (ε 20,000). However, we were able to make measurements on solutions of some of the bases in concentrated sulphuric acid. The spectra (see Table 4) are simpler than those observed for other solvents and show very broad maxima. It may

TABLE 4. *Light absorptions in concentrated sulphuric acid.*

Compound	$\lambda_{max.}$ (Å)	ε	Compound	$\lambda_{max.}$ (Å)	ε
(I*b*	2445	55,900	(I*c*)	2435	84,000
	3605	27,500		3690	33,400
		(4,800 at 4000 Å)			(21,800 at 4000 Å
					3,400 at 4900 Å)
(IV; R′ = Ph, R″ = H)	2375	28,300			
	3695	14,700			
		(9,600 at 4000 Å)			

be concluded that the benzene and the naphthalene macrocycle, and diphenyliminoisoindoline, have analogous structures in sulphuric acid solution. The common chromophore appears to be that of aminoimino*iso*indolenine (IV*B*), which doubtless is doubly protonated; the preparation (in the absence of water) of a dihydrochloride of di-imino*iso*indoline (*J.*, 1952, 5000) shows this to be feasible.

EXPERIMENTAL

Preparation of the Macrocycles.—(i) *The benzene macrocycle* (I*b*). 1 : 3-Di-imino*iso*indoline (13·6 g.) and *m*-phenylenediamine (10 g.; purified) were heated together in boiling ethanol (or butanol) (200 c.c.) for 17 hr., during which ammonia was evolved. After being washed with

ethanol, the yellow solid (15·7 g., 71%) had m. p. 375°. From nitrobenzene, the benzene *macrocycle* (I*b*) crystallised as very small yellow needles, m. p. 380°; sublimation in nitrogen at 340°/15 mm. gave needles several mm. long [Found: C, 76·8; H, 4·2; N, 19·0%; *M* (ebullioscopic in nitrobenzene), 380, 472, 407. $C_{28}H_{18}N_6$ requires C, 76·7; H, 4·1; N, 19·2%; *M*, 438].

(ii) *The naphthalene macrocycle* (I*c*). Similarly, the di-imine (9·2 g.) was heated with 2 : 7-diaminonaphthalene (10 g.) in boiling ethanol (or butanol) (100 c.c.), and the yellow product (14 g., 82%) washed well with ethanol. Several extractive crystallisations (Soxhlet) with pyridine, and sublimation at 400—450°/15 mm., afforded fine yellow needles, m. p. *ca.* 500° (decomp.), of the naphthalene *macrocycle* (I*c*) [Found: C, 80·35; H, 4·1; N, 15·5%; *M* (ebullioscopic in nitrobenzene), 561, 532. $C_{36}H_{22}N_6$ requires C, 80·3; H, 4·1; N, 15·6%; *M*, 538].

(iii) *The acridine macrocycle* (I*d*). From the di-imine (5·8 g.) and 2 : 8-diaminoacridine (8·36 g.) in boiling butanol (100 c.c.), ammonia was evolved and a brown product (8·5 g.) separated. After being washed with butanol and ether, and extractively crystallised (Soxhlet) several times from pyridine, the acridine *macrocycle* (I*d*) formed deep-yellow rods with a bronze lustre (2·4 g., 18%), which gradually decomposed at >400° (Found: C, 78·6; H, 4·2; N, 17·6. $C_{42}H_{24}N_8$ requires C, 78·7; H, 3·8; N, 17·5%).

(iv) *The* 3 : 5-*pyridine macrocycle* (I*e*). A solution of the di-imine (1·5 g.) and 3 : 5-diaminopyridine (1 g.) in butanol (20 c.c.) was boiled for 17 hr. (ammonia evolved) and then cooled. Crystallisation of the solid (1·88 g.) from nitrobenzene afforded the 3 : 5-pyridine *macrocycle* (I*d*) (925 mg., 46%) as very small yellow needles, m. p. 436° (decomp.) (Found: C, 70·7; H, 3·9; N, 25·9. $C_{26}H_{16}N_8$ requires C, 70·9; H, 3·7; N, 25·5%).

Hydrolysis of the Macrocycles.—(i) The benzene macrocycle (I*b*) (0·1 g.) was recovered after being boiled with a mixture of concentrated hydrochloric acid (10 c.c.) and glacial acetic acid (10 c.c.) for 2 hr. When the benzene macrocycle (0·5 g.), concentrated hydrochloric acid (10 c.c.) and acetic acid (10 c.c.) were heated together at 150° for 7 hr. and the solution cooled, phthalic acid separated [0·23 g.; m. p. 196—197° (decomp.)]. The filtrate was evaporated to dryness, and the residue taken up in cold water (3 c.c.), undissolved phthalic acid (0·13 g.) being collected (total yield of phthalic acid, 0·36 g., 1·90 mols.; *S*-benzylthiuronium salt, m. p. and mixed m. p. 158—159°). The filtrate was added to picric acid (0·65 g.) in water (65 c.c.), the mixture was chilled in ice, and the *m*-phenylenediamine picrate collected, washed with water, and dried [yield, 0·69 g., 1·79 mols.; m. p. and mixed m. p. 181° (decomp.)].

(ii) The naphthalene macrocycle (0·5 g.) was not hydrolysed by a mixture of concentrated hydrochloric acid (10 c.c.) and acetic acid (10 c.c.) at 150° for 4 hr.; heating at 180° for 15 hr. was necessary for the degradation. The dark solution was evaporated to dryness and the residue warmed with N-sodium hydroxide (10 c.c.) for 10 min., during which ammonia was evolved. The mixture was cooled in ice, and 2 : 7-diaminonaphthalene (0·27 g., 1·84 mols.) collected [picrate, m. p. and mixed m. p. 209° (decomp.)]. Acidification of the filtrate with concentrated hydrochloric acid caused precipitation of phthalic acid [0·26 g., 1·68 mols., m. p. 195—196° (decomp.); *S*-benzylthiuronium salt, m. p. and mixed m. p. 158°].

(iii) The acridine macrocycle (I*d*) (220 mg.) was boiled with concentrated hydrochloric acid (10 c.c.) for *ca.* 15 min. The solution was evaporated to dryness, the residue warmed with 2N-sodium hydroxide (10 c.c.), the 2 : 8-diaminoacridine was collected [139 mg., 1·93 mols.; m p. and mixed m. p. (sealed tube) 275°], and the filtrate evaporated to small bulk and acidified with concentrated hydrochloric acid. Phthalic acid separated [93 mg., 1·63 mols., m. p. 191° (decomp.); *S*-benzylthiuronium salt, m. p. and mixed m. p. 158—159°].

(iv) The 3 : 5-pyridine macrocycle (205 mg.) was heated under reflux with 2N-hydrochloric acid (10 c.c.) for *ca.* 30 min., and the solution was filtered from a trace of a dark material, and evaporated to dryness. Trituration of the residue with water (2 c.c.) afforded phthalic acid (138 mg., 1·78 mols.), m. p. 195° (decomp.); *S*-benzylthiuronium salt, m. p. and mixed m. p. 159°. A further portion of the macrocycle (223 mg.) was similarly hydrolysed and the solution evaporated. Excess of aqueous sodium hydroxide was added and, by continuous extraction of the solution with benzene, 3 : 5-diaminopyridine (90·5 mg., 1·64 mols.) was isolated, m. p. and mixed m. p. 112—113°.

Hydrochlorides of the Macrocycles.—(i) Addition of ethanolic hydrogen chloride to a solution of the benzene macrocycle (200 mg.) in ethanol (200 c.c.) caused precipitation of the infusible orange-red *dihydrochloride* (220 mg., 94%), which was collected and washed with ethanol by centrifugation (Found: Cl, 12·8. $C_{28}H_{20}N_6Cl_2$ requires Cl, 13·9%). Treatment with sodium hydroxide regenerated the macrocycle, m. p. and mixed m. p. 380°.

(ii) Similarly from the naphthalene macrocycle in dioxan, the scarlet *dihydrochloride* was obtained (Found : Cl, 11·5. $C_{36}H_{24}N_6Cl_2$ requires Cl, 11·6%), from which sodium hydroxide regenerated the yellow macrocycle, m. p. *ca.* 500° (decomp.).

(iii) Trituration of the acridine macrocycle (53 mg.) with concentrated hydrochloric acid (5 c.c.) for 5 min. gave a dark hydrochloride (60 mg.), which was washed with concentrated hydrochloric acid, methanol, and ether [Found, after being dried (*a*) at 10^{-5} mm. for 8 hr. and (*b*) at 200°/10^{-4} mm. for 3 hr. : Cl, (*a*) 12·85, (*b*) 7·4. Calc. for $C_{42}H_{27}N_8Cl_3$: Cl, 14·2. Calc. for $C_{42}H_{26}N_8Cl_2$: Cl, 9·9%].

(iv) When the 3 : 5-pyridine macrocycle (70 mg.) was stirred with 2N-hydrochloric acid for 5 min., the salmon-pink *dihydrochloride* (76 mg.) separated (Found : Cl, 13·7. $C_{26}H_{18}N_8Cl_2$ requires Cl, 13·8%).

Compounds of the Macrocycles with Acetic Acid.—(i) The benzene macrocycle (291 mg.) was dissolved in boiling glacial acetic acid (15 c.c.), and the red solution evaporated to 5 c.c. The *triacetate* (381 mg.) separated as orange rhombs, which were dried at 10^{-6} mm. for 3 hr. (Found : C, 65·7; H, 5·3; N, 14·0. $C_{28}H_{18}N_6,3C_2H_4O_2$ requires C, 66·0; H, 4·9; N, 13·6%). The compound lost acetic acid at 155° and reverted to the macrocycle.

(ii) When boiled with acetic acid (20 c.c.) for 30 min., the naphthalene macrocycle (102·5 mg.) was converted into an orange product (159 mg.) (Found : C, 69·1; H, 5·05; N, 13·8. Calc. for $C_{36}H_{22}N_6,2C_2H_4O_2$: C, 72·9; H, 4·6; N, 12·8. Calc. for $C_{36}H_{22}N_6,C_2H_4O_2,3H_2O$: C, 69·9; H, 4·9; N, 12·9%), which lost acetic acid at 175—180°.

(iii) A solution of the acridine macrocycle (144 mg.) in boiling acetic acid (15 c.c.) deposited a red *triacetate dihydrate* (Found : C, 66·5; H, 5·1; N, 13·8. $C_{42}H_{24}N_8,3C_2H_4O_2,2H_2O$ requires C, 67·3; H, 4·7; N, 13·1%).

(iv) The 3 : 5-pyridine macrocycle (33 mg.) was dissolved in hot acetic acid (5 c.c.), and the filtered solution evaporated to 1 c.c. Orange crystals (26 mg.) of the *diacetate* slowly separated (Found, after being dried over KOH : C, 63·7; H, 4·4; N, 20·5. $C_{26}H_{16}N_8,2C_2H_4O_2$ requires C, 64·3; H, 4·3; N, 20·0%).

Compounds of the Macrocycles with Methyl Iodide.—(a) *Preparations.* The 3 : 5-pyridine macrocycle was heated with a large excess of purified methyl iodide in a sealed glass tube (air removed) at 100° for 24 hr. The *dimethiodide* was an orange infusible powder (Found : I, 34·65. $C_{28}H_{22}N_8I_2$ requires I, 35·0%).

Similarly obtained were the orange-red benzene macrocycle *dimethiodide* (Found : I, 36·8. $C_{30}H_{24}N_6I_2$ requires I, 35·1%), the crimson naphthalene macrocycle *dimethiodide* (Found : I, 29·9. $C_{38}H_{28}N_6I_2$ requires I, 30·85%), and a dark product from the acridine macrocycle (Found : I, 22·2. Calc. for $C_{42}H_{24}N_8,2MeI$: I, 27·45%).

(b) *Hydrolyses.* (i) The 3 : 5-pyridine macrocycle dimethiodide (295 mg.) was warmed with 2N-hydrochloric acid (10 c.c.) on the steam-bath until hydrolysis was complete. The solution was then evaporated, and a filtered aqueous extract (3 c.c.) of the residue was treated with an excess of aqueous picric acid. 3 : 5-Diamino-1-methylpyridinium picrate (250 mg., 1·74 mols.) separated, m. p. 200—201° after recrystallisation from water. The m. p. was not depressed by authentic material, described below.

(ii) The acridine macrocycle methiodide (341 mg.) was boiled with 15% aqueous hydrochloric acid for 1 hr., and the red solution was filtered and cooled. The orange product (a hydrochloride) (276 mg.), after several crystallisations from 15% hydrochloric acid, had m. p. >360° (Found : C, 53·3; H, 5·5; H, 14·35%). Light absorption in ethanol : max. at 2630, 2800, 4600 Å (ε 1650, 780, 1300). Acriflavine, recrystallised similarly, formed orange-red crystals, m. p. *ca.* 255° (decomp.). Light absorption in EtOH (at same concentration as preceding substance) : max. at 2620, 2820, 4650 Å (ε 1980, 820, 1700). 2 : 8-Diaminoacridine hydrochloride crystallised from 15% hydrochloric acid as a very dark brown microcrystalline powder, m. p. >300°.

(c) *Action of alkali.* (i) A suspension of the benzene macrocycle dimethiodide (544 mg.) in 2N-sodium hydroxide (10 c.c.) was warmed until the solid had become yellow. The methohydroxide was collected and washed with water. The filtrate and washings were treated with 2N-nitric acid and an excess of aqueous silver nitrate, whereupon silver iodide was precipitated (387 mg., 2·18 mols.). The yellow methohydroxide dissolved easily in methanol, and on concentration of the solution yellow needles separated, having m. p. 360—361°; these effloresced rapidly in the air to a yellow methanol-insoluble powder, m. p. 380° undepressed by the parent benzene macrocycle. Addition of iodine-free hydriodic acid to a methanolic solution of the methohydroxide caused precipitation of the orange dimethiodide (identified by its behaviour with alkali). The benzene macrocycle *dihydriodide* was a maroon-coloured powder, m. p.

>500° (Found : I, 33·6. $C_{28}H_{20}N_6I_2$ requires I, 36·6%), which with 2N-sodium hydroxide at once gave the benzene macrocycle, m. p. and mixed m. p. 379°. When kept under methanol for several days, the benzene macrocycle was transformed into beautiful yellow needles of the sparingly soluble *dimethanol* solvate which was stable in the air; when a portion (92·8 mg.) was heated at 100°/0·1 mm. for 1 hr., it lost the solvent (Found : loss in wt., 10·5. $C_{28}H_{16}N_6$,2MeOH requires MeOH, 12·7%) and gave back the macrocycle (84·0 mg.).

(ii) Treatment of the naphthalene macrocycle dimethiodide (817 mg.) with boiling 2N-sodium hydroxide (10 c.c.) slowly gave a yellow solid (530 mg.), m. p. *ca.* 500°, indistinguishable from the parent naphthalene macrocycle. From the filtrate, silver iodide was precipitated (313 mg., 1·34 mols.).

Attempted Preparation of Metal Derivatives of the Macrocycles.—(i) Hot solutions of the benzene macrocycle (127 mg.) and cobalt acetate (77 mg.) in dimethylformamide (3-c.c. portions) were mixed. After evaporation of the solvent, and washing of the residue with methanol, unchanged macrocycle (117 mg.) was recovered, m. p. 380°. Similar results were obtained with nickel, copper, and zinc acetate. The naphthalene macrocycle likewise failed to yield a metal derivative.

(ii) A solution of the acridine macrocycle (14·8 mg.) in hot dimethylformamide (20 c.c.), treated with cobalt acetate (25·7 mg.) or copper or nickel acetate in the same solvent (2 c.c.), and then cooled, deposited orange crystals (12 mg.) of the *solvated* acridine macrocycle (metal-free borax bead), also obtained in the absence of metal salts (Found : C, 70·5; H, 5·1; N, 16·6. $C_{42}H_{24}N_8$,2H·CO·NMe_2,2H_2O requires C, 70·0; H, 5·1; N, 17·0%). The solvate evolved liquid and became lighter in colour at 150°, the residue decomposing at >400°. When heated at 200°/0·1 mm. for 2 hr., the solvate (63·6 mg.) was reconverted into the acridine macrocycle (49·3 mg., 1 mol.) (Found : N, 17·2. Calc. for $C_{42}H_{24}N_8$: N, 17·5%).

(iii) Mixing of solutions of the 3 : 5-pyridine macrocycle (65·7 mg.) and copper acetate (62·7 mg.) in dimethylformamide (5-c.c. portions) caused precipitation of a brown, amorphous, infusible *copper* complex (54·3 mg.) (Found : C, 48·9; H, 4·0; N, 15·5; Cu, 18·0. $C_{30}H_{28}O_7N_8Cu_2$ requires C, 48·7; H, 3·8; N, 15·2; Cu, 17·2%).

Addition of zinc acetate (61 mg.) in dimethylformamide (0·5 c.c.) to the 3 : 5-pyridine macrocycle (53 mg.) in the same solvent (3 c.c.) gave, during 24 hr., a yellow amorphous precipitate of the *zinc* complex (90·8 mg.) (Found : C, 48·5; H, 3·8; N, 13·9, 14·0; Zn, 17·5. $C_{30}H_{28}O_7N_8Zn_2$ requires C, 48·5; H, 3·8; N, 15·1; Zn, 17·6%).

3 : 5-*Diamino*-1-*methylpyridinium Picrate.*—3 : 5-Diaminopyridine (0·1 g.) was warmed with an excess of methyl iodide for 5 min., and the solution evaporated. The residue was taken up in ethanol (10 c.c.) and ethanolic picric acid added. 3 : 5-*Diamino*-1-*methylpyridinium picrate* crystallised from water and had m. p. 201° (decomp.) (Found : C, 40·9; H, 3·9; N, 23·75. $C_{12}H_{12}O_7N_6$ requires C, 40·9; H, 3·4; N, 23·9%).

We gratefully acknowledge a maintenance grant (to P. F. C.) from the Ministry of Education, and gifts of chemicals from Imperial Chemical Industries Limited, Dyestuffs Division. Microanalyses were performed in the Micro-analytical Laboratory (Mr. F. H. Oliver), and measurements of light absorption in the Spectrographic Laboratory (Mrs. A. I. Boston) of this Department.

Department of Organic Chemistry, Imperial College of Science and Technology,
South Kensington, London, S.W.7. [*Received, March 20th*, 1954.]

Optical Activity in 1-*Phenylnaphthalene-2′-carboxylic Acid and Related Compounds.*

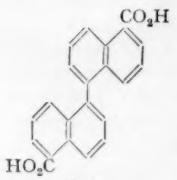
By D. Muriel Hall, S. Ridgwell, and E. E. Turner.

[Reprint Order No. 5136.]

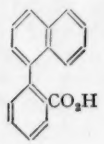
1-Phenylnaphthalene-2′-carboxylic acid and -2′ : 8-dicarboxylic acid have been obtained optically active. The active acids racemise in " B.P. " chloroform solution at 20° with half-life periods of 2 and 60 minutes respectively. The salts of these acids can undergo first- and second-order asymmetric transformations. The racemisation rates of 1 : 1′-dinaphthyl-5 : 5′- and -8 : 8′-dicarboxylic acid in aqueous sodium hydroxide solution have been compared.

Diphenic acid undergoes rapid optical activation at −30° in chloroform solution in the presence of (+)-nor-ψ-ephedrine (Lesslie, Turner, and Winton, *J.*, 1951, 257), but the free acid has never been obtained optically active. Bell, Morgan, and Smyth (*Chem. and Ind.*, 1951, 634) recorded the isolation of optically active 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid (I*a* and I*b*) with $[\alpha]_D$ +66° in 0·1N-sodium hydroxide. The activity was said to be lost when the solution " was boiled for an hour." The relatively high optical stability suggested by this statement is surprising, since, although the 8- and the 8′-carbon atom clearly cannot pass each other without great distortion of the main structure (I*a*), very little interference would hitherto have been expected between the hydrogen atoms in the 2- and 8′- or in the 2′- and 8-positions (I*b*). Bell and his co-workers (*loc. cit.*; Crawford and Smyth, *J.*, 1952, 4133) also obtained 4 : 4′-diquinolyl and 5 : 5′-diquinolyl in optically active but evidently less optically stable forms. They associated the optical activity observed in these three compounds with steric interaction between the van der Waals envelopes of the 2- and the 8′-hydrogen atom.

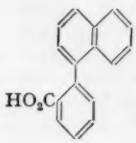
(I*a*)



(I*b*)



(II*a*)



(II*b*)

In order to obtain a more quantitative assessment of the optical stability of 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid, we have examined the acid in some detail. A brucine salt was obtained from aqueous 2-ethoxyethanol, and gave rise to an active acid with a half-life of 33 minutes in 0·1N-sodium hydroxide, at 60°.

An acid intermediate between diphenic acid and 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid might be expected to be capable of exhibiting optical activity. Such an acid, 1-phenylnaphthalene-2′-carboxylic acid (II*a* and *b*) has been examined. In acetone solution, second-order asymmetric transformation was realised with cinchonidine and with brucine. The brucine (+)-acid salt had a half-life of 0·6 minute in chloroform solution at 20° and yielded optically active (+)-1-phenylnaphthalene-2′-carboxylic acid which had a half-life of 2 minutes in chloroform solution at 20°. Optical activation of the (±)-acid was observed in presence of three alkaloids in chloroform solution; with brucine the value for k of first-order asymmetric transformation was the same as that for the mutarotation of the salt obtained by second-order asymmetric transformation. The acid was activated by cinchonidine in chloroform but not in acetone solution.

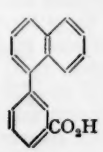
For one position of the phenyl nucleus (as in II*a*), rotation about the 1 : 1′-bond is effectively prevented by interference between the carboxyl group and the 8-CH grouping. In the other position (as in II*b*), however, hindrance to rotation arises from the slight overlap of the 2′- and the 8-hydrogen atoms. The present results therefore support the assump-

tion that hydrogen atoms are capable of impeding free rotation when they are attached to an aromatic nucleus.

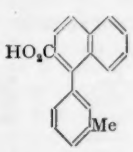
In order to investigate some of the limits of this effect, we examined 1-phenylnaphthalene-3'-carboxylic acid (III) and 3'-methyl-1-phenylnaphthalene-2-carboxylic acid (IV), in both of which the maximum blocking is provided by the slight overlap of the 2'- (or 6'-) and the 8-hydrogen atoms. With neither acid could evidence of optical activity be obtained, either by " addition curve " technique (Jamison and Turner, *J.*, 1938, 1646; 1940, 264) or by the achievement of a second-order asymmetric transformation. It may be noted that although (IV) appears similar to (II*b*), there is no position of (IV) comparable to (II*a*), in which passing of the *ortho*-groups is effectively prevented.

Evidently, therefore, in the series now under discussion, interference between the two nuclear hydrogen atoms, *without supporting collisions between other groups* in the molecule, does not hinder rotation about the 1 : 1'-bond sufficiently to give rise to observable optical activity.

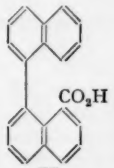
A comparative study of the relative optical stabilities of 1 : 1'-dinaphthyl-5 : 5'-dicarboxylic acid (I*a* and I*b*), 1 : 1'-dinaphthyl-8-carboxylic acid (V), and 1 : 1'-dinaphthyl-8 : 8'-dicarboxylic acid (VI) reveals an apparent anomaly. Meisenheimer and Beisswenger (*Ber.*, 1932, **65**, 32) resolved (V) and (VI) and determined the rates of racemisation of the acids in aqueous sodium hydroxide solution (see also Stanley, *J. Amer. Chem. Soc.*, 1931, **53**, 3104). The half-life periods found were : (V) 15 hours at 20° and (VI) 160 minutes at 20°, so that the order of stabilities appears to be (V) > (I) > (VI). [The half-life of (I) at 20° is not known, but an estimation from the value at 60° indicates that it will be between 300 and 700 minutes.] This order seemed to be contrary to expectation, and we therefore reinvestigated (VI) : our results agree closely with those of Meisenheimer. The order is no longer anomalous, however, if the stability of the monoethyl ester of (VI) is considered. Meisenheimer showed this compound to possess a half-life of 28 hours in aqueous sodium hydroxide at 18°. We thus have for stability order : Monoethyl ester of (VI) > (V) > (I). It appears to follow that the relatively low optical stability of the disodium salt of (VI) is due to the presence in the molecule of the two charged carboxylate ion groups in blocking positions. Even so, it is difficult to see why (VI) or its monoethyl ester should racemise at all readily. It appears from models that the considerable interference with free rotation about the 1 : 1'-bond in 1 : 1'-dinaphthyl-8 : 8'-dicarboxylic acid is similar to that in 1 : 1'-dinaphthyl-2 : 2'-dicarboxylic acid. But the latter compound is highly optically stable. Kuhn and Albrecht (*Annalen*, 1928, **465**, 282) failed to racemise it on heating a solution in aqueous sodium hydroxide solution for 4½ hours on a boiling water-bath; we resolved the acid for another purpose (Hall and Turner, *Chem. and Ind.*, 1953, 1177) and confirmed this result. The rotation of the acid was unchanged after boiling in 0·1N-sodium hydroxide for 10 hours, followed by heating at 140° in a sealed tube for 5 hours.



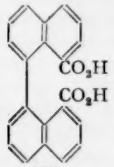
(III)



(IV)



(V)



(VI)

Attention may be drawn to the fact that certain active substituted diphenic acids are known for which the rates of racemisation in aqueous sodium hydroxide are greater than those in an organic solvent. Stanley, McMahon, and Adams (*J. Amer. Chem. Soc.*, 1933, **55**, 706) observed that 6 : 6'-dimethoxydiphenic acid (VII) racemised in boiling sodium ethoxide solution with a half-life of 11 hours, and in boiling 0·1N-sodium hydroxide with a half-life of 7 hours 50 minutes, whilst in boiling ethyl alcohol the half-life was 61·5 hours. Adams and Hale (*ibid.*, 1939, **61**, 2825) recorded that whilst 6-nitrodiphenic acid (VIII) racemised in boiling 0·1N-sodium hydroxide with a half-life of 4·6 minutes, the half-life of the acid in boiling *n*-butyl alcohol was 101 or 107 minutes.

We have also examined 1-phenylnaphthalene-2′ : 8-dicarboxylic acid (IX*a* and *b*). The brucine salt of this acid underwent first-order asymmetric transformation in chloroform solution at 20°. With two molecules of brucine to one of acid the rate of equilibration was considerably faster than with one molecule of each. Second-order transformation in benzene solution gave a monobrucine (+)-acid salt (even when two equivalents of brucine were used), having a half-life of 460 minutes in chloroform solution at 20°. Racemisation of the free (+)-acid was observed in chloroform solution at 20°; the rate of racemisation was very sensitive to the presence of small quantities of ethyl alcohol, and half-life periods of 35 minutes (most alcohol), 60 minutes, and 220 minutes (least alcohol) were observed. This acid is thus intermediate in optical stability between 1-phenylnaphthalene-2′-carboxylic acid and 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid. It was not possible to observe racemisation in alkaline solution. The sodium salt is sparingly soluble and the acid

FIG. 1. FIG. 2.

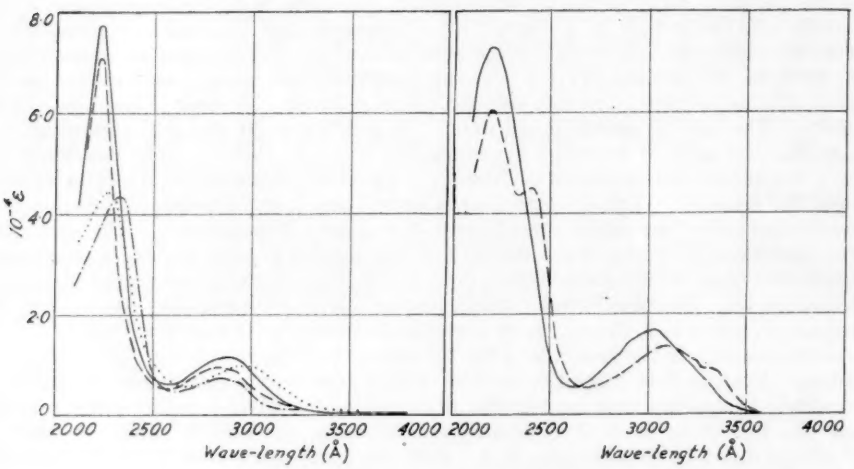


FIG. 1. ———— 1-*Phenylnaphthalene-3′-carboxylic acid* (III).
— — — — 1-*Phenylnaphthalene-2′-carboxylic acid* (II).
— · — · — 3′-*Methyl*-1-*phenylnaphthalene-2-carboxylic acid* (IV).
. . . . . 1-*Phenylnaphthalene-2′* : 8-*dicarboxylic acid* (IX).
FIG. 2. ———— 1 : 1′-*Dinaphthyl-5* : 5′-*dicarboxylic acid* (I).
— — — — 1 : 1′-*Dinaphthyl-8* : 8′-*dicarboxylic acid* (VI).

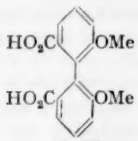
Ultra-violet absorption spectra.

	Short-wave band				Long-wave band	
Compound	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{max.}$	$\varepsilon_{max.}$
(I)	2216	74,000	2602	4800	3022	16,500
(VI)	2195	60,000	2675	4800	3092	13,800
	2395	44,500	—	—	3320	9,400
(II)	2225	68,500	2560	5100	2835	9,200
(III)	2230	77,500	2555	5400	2890	11,100
(IV)	2325	43,000	2600	3750	2840	6,800
(IX)	2262	43,500	2672	4900	2987	9,300

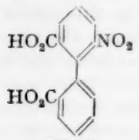
dissolves so slowly in aqueous potassium hydroxide solution that polarimetric readings could not be taken until 15 minutes after wetting, by which time racemisation was complete. This result indicates qualitatively, however, that, as with (VI), the anion racemises faster than the free acid.

The ultra-violet absorption spectra of the acids (I—IV, VI, and IX) have been measured in 96% ethanol and the main features are recorded in the Table and in Figs. 1 and 2. The spectra of compounds (I) and (VI) differ from the spectrum of 1 : 1′-dinaphthyl, and those

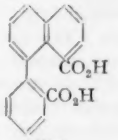
of (II), (III), and (IX) from that of 1-phenylnaphthalene to extents which are, in general, consistent with the expected effects of the substituents on the spectra of the parent compounds (Hirshberg and Jones, *Canad. J. Res.*, 1949, **27**, *B*, 437) and on the steric hindrance to coplanarity across the 1 : 1'-bonds (Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199). The low band intensities and the short-wave shift of the long-wave band in the spectrum of (IV) appear to be anomalous. There is a poor correlation between the



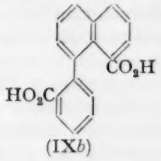
(VII)



(VIII)



(IX*a*)



(IX*b*)

relative degrees of conjugation across the 1 : 1'-bond, as inferred from the spectra, and the relative optical stabilities of the active isomers. The latter seem to be determined by the gross steric hindrance to coplanarity across the 1 : 1'-bond, in terms of the number and location of the adjacent substituent groups. The secondary effects of the substituents on the conjugation, and hence on the length of this bond, do not appear to have any further influence on the ease of rotation about it. This conclusion is contrary to the view taken by Calvin (*J. Org. Chem.*, 1939, **4**, 256) who has suggested that the shortening of the 1 : 1'-bond in diphenyls by resonance interaction of the appropriate 4 : 4'-substituents may be an important factor in determining optical stability. The lack of correlation between the spectra and optical stabilities of our compounds may perhaps be associated with the possibility that some of the compounds have non-coplanar ground states and coplanar excited stated (cf. Braude, Sondheimer, and Forbes, *Nature*, 1954, **173**, 117), so that the substituents affect the spectra by altering the transition probabilities for the excited states and have little influence on the ground states.

It may be pointed out that the interpretation of the spectra is almost certainly complicated by the sensitivity of the long-wave fine-structure to the state of ionisation of the carboxyl groups. Detailed studies of this effect and spectrophotometric measurements of p*K*'s are envisaged. The results should provide additional evidence on the coplanarity or otherwise of the carboxyl groups with the aromatic rings to which they are attached.

Experimental

In all polarimetric observations $l = 2$ unless otherwise stated.

5-Amino-1-naphthoic Acid.—This was prepared as described by Ekstrand (*J. pr. Chem.*, 1888, **38**, 241). More precise conditions for the nitration of 1-naphthoic acid were worked out. Finely ground 1-naphthoic acid (90 g.) was added gradually with stirring to nitric acid (*d* 1·42; 600 c.c.) at 80° and heating continued for a further ½ hr. The cooled solution was poured on ice, and a small quantity of 1-nitronaphthalene removed by treating the product with sodium carbonate solution and reprecipitating the mixed 5- and 8-nitronaphthoic acids. Two recrystallisations from ethanol gave 5-nitro-1-naphthoic acid (20 g., 16%) with m. p. 238—239°.

1 : 1'-*Dinaphthyl*-5 : 5'-*dicarboxylic Acid* (I).—This was prepared from 5-amino- *via* 5-iodo-1-naphthoic acid as described by Seer and Scholl (*Annalen*, 1913, **398**, 82). After the methyl ester had been heated with copper bronze in an atmosphere of carbon dioxide the mixture was extracted whilst hot with *o*-dichlorobenzene, and the crude ester was hydrolysed. 1 : 1'-Dinaphthyl-5 : 5'-dicarboxylic acid, crystallised twice from ethanol, had m. p. 358° (block) (50% yield).

Brucine Salt of (+)-1 : 1'-*Dinaphthyl*-5 : 5'-*dicarboxylic Acid.*—The acid (0·684 g., 1 mol.) and anhydrous brucine (1·576 g., 2 mols.) were dissolved in boiling 2-ethoxyethanol (40 c.c.), and hot water (80 c.c.) was added. The solution was boiled and cooled. It deposited prisms (1·29 g., 58% of total solid). From the re-heated mother-liquor a further 0·32 g. was obtained by the addition of water.

(+)-1 : 1'-*Dinaphthyl*-5 : 5'-*dicarboxylic Acid.*—The first crop of salt was ground with hydrochloric acid and dissolved in 0·1N-sodium hydroxide, and the solution was shaken with chloroform to remove traces of brucine. The solution had α^{20}_{5461} +0·51°. Its concentration was determined by precipitation of the acid from a known volume; the acid was thus found to have $[\alpha]^{20}_{5461}$

+27·2° (*c*, 0·8260 in 0·1N-sodium hydroxide). Racemisation at 60° gave $k = 0·024$ min.$^{-1}$. Similar treatment of the second crop gave acid with $[\alpha]^{20}_{5461}$ +56·1° (*c*, 0·3210 in 0·1N-sodium hydroxide), *k* for racemisation at 60°, 0·020 min.$^{-1}$.

In a second series of experiments, crystallisation of the brucine salt was brought about at 80° by gradual addition of water to a solution in 2-ethoxyethanol. The first crop (45·5% of total solid) had $[\alpha]^{20}_{5461}$ −16·3° in $CHCl_3$ and gave an acid with $[\alpha]^{20}_{5461}$ +56·6° in 0·1N-sodium hydroxide. A second crop (33·4% of total solid) was obtained by adding more water at 80° and allowing the solution to cool. It had $[\alpha]^{20}_{5461}$ −23·1° in chloroform and gave an acid with $[\alpha]^{20}_{5461}$ +45·3° in 0·1N-sodium hydroxide. For these two acids the rate constants of racemisation at 60° in 0·1N-sodium hydroxide were, respectively, $k = 0·019$ and 0·020 min.$^{-1}$.

The average value of *k* from all these racemisations is 0·020 min.$^{-1}$, whence half-life = 33 min.

1-*Phenylnaphthalene*-2′-*carboxylic Acid* (II).—This was prepared by heating a mixture of 1-iodonaphthalene, methyl *o*-iodobenzoate, and copper bronze and hydrolysing the product (Baddar and Warren, *J.*, 1938, 401). The acid had m. p. 159·5—161°.

Second-order Asymmetric Transformation of Brucine Salt.—1-Phenylnaphthalene-2′-carboxylic acid (1·5081 g., 1 mol.) and anhydrous brucine (2·5100 g., 1 mol.) were dissolved together in 100 c.c. of boiling acetone. The solution was filtered hot and the filtrate evaporated to about 30 c.c. The crystalline material which separated was filtered, washed with acetone, and dried in a vacuum [yield 3·66 g., representing 91% of the total solids originally taken; m. p. 105° (decomp.)].

The mutarotation of the brucine (+)-acid salt was twice followed in " B.P. " chloroform at 20°. Readings were started (1) 1·75 min. and (2) 2·1 min. respectively after wetting of the solids with solvent.

Experiment (1).

Time after wetting with solvent (min.)	1·75	2·2	2·7	3·3	4·1	4·75	12·0	∞
α^{20}_{5461}	+0·03	−0·10	−0·20	−0·26	−0·30	−0·31	−0·32	−0·32
k (min.$^{-1}$)	—	1·03	1·13	1·14	1·22	1·18	—	—

Average *k*, 1·1 min.$^{-1}$, whence half-life = 0·6 min.

(+)-1-*Phenylnaphthalene*-2′-*carboxylic Acid.*—The brucine (+)-acid salt was ground with excess of formic acid at about 5°. The suspension was poured into a large bulk of ice-cold dilute hydrochloric acid. The precipitated (+)-*acid*, washed and dried in a vacuum, had m. p. 162° (Found: C, 82·15; H, 4·9. $C_{17}H_{12}O_2$ requires C, 82·2; H, 4·9%).

Racemisation of (+)-1-*Phenylnaphthalene*-2′-*carboxylic Acid.*—A solution (20 c.c.) of the acid (0·2130 g.) in " B.P. " chloroform was studied at 20° on two separate occasions. *k* found: (1) 0·355, (2) 0·36 min.$^{-1}$, whence average half-life = 2·0 min.

Second-order Asymmetric Transformation of Cinchonidine Salt.—The acid (0·2462 g., 1 mol.) and cinchonidine (0·2942 g., 1 mol.) were dissolved together in 2·5 c.c. of boiling acetone. The (filtered) solution deposited 0·425 g. of *salt* (77% of total), m. p. 148—150° (decomp.) (Found: C, 79·7; H, 6·3. $C_{36}H_{34}O_3N_2$ requires C, 79·0; H, 6·3%). The mutarotation of the salt was followed in chloroform solution at 20°. The observed angle changed from 5·07° to 4·33°. $k = 1·3$ min.$^{-1}$, half-life = 0·5 min.

First-order Asymmetric Transformations.—(a) *With brucine.* A chloroform solution was made up to contain 0·1546 g. (1 mol.) of (±)-acid and 0·2455 g. (1 mol.) of anhydrous brucine in 20 c.c. at 20°. The solution was examined polarimetrically, the first reading being made 1·6 min. after wetting. The observed angle of rotation changed from −0·40° to −0·31° during 4 min. A second experiment gave similar figures, and the log plot of the combined readings gave a value of *k* approximately equal to the more accurate one derived from the second-order asymmetric transformation.

(b) *With cinchonidine.* A chloroform solution (20 c.c.) containing the (±)-acid (0·1415 g.) and cinchondine (0·1676 g.) was examined at 20°; α^{20}_{5461} changed from +4·18° to +4·32° in about 3 min.

(c) *With quinidine.* A solution (25 c.c.) of the (±)-acid (0·2014 g.) and quinidine (0·2627 g.) in chloroform mutarotated through +0·10°.

1-*Phenylnaphthalene*-3′-*carboxylic Acid* (III).—Copper bronze (27 g., 6 atom-equiv.) was added gradually to a stirred mixture of 1-iodonaphthalene (18·2 g., 1 mol.) and methyl *m*-iodobenzoate (18·8 g., 1 mol.) at 270°. The temperature rose to 300°. After ½ hr. the mixture was allowed to cool to 150° and extracted with hot *o*-dichlorobenzene. After removal of the solvent, the residual oil was hydrolysed by boiling with 10% alcoholic potassium hydroxide (200 c.c.) for

6 hr. The alcohol was removed and the residue extracted with water. After being shaken with benzene, the aqueous extract was acidified, and the precipitated acids were extracted with cold benzene. The benzene was removed, and the residue crystallised four times from methanol. 1-*Phenylnaphthalene-3'-carboxylic acid* (3·2 g., 17%) was obtained as prisms, m. p. 185·5—188° (Found: C, 82·2; H, 5·2. $C_{17}H_{12}O_2$ requires C, 82·2; H, 4·9%).

Brucine Salt of 1-*Phenylnaphthalene-3'-carboxylic Acid.*—The acid (0·1000 g., 1 mol.) and anhydrous brucine (0·1184 g., 1 mol.) were dissolved in boiling *cyclo*hexane (80 c.c.). The cooled solution deposited the *salt* (0·2000 g.), m. p. 144° (decomp.) (Found: C, 74·5; H, 6·5; N, 4·0. $C_{40}H_{38}O_6N_2$ requires C, 74·8; H, 6·0; N, 4·4%). The salt showed no mutarotation at 5° in chloroform solution, and on decomposition gave an inactive acid.

3'-Methyl-1-phenylnaphthalene-2-carboxylic Acid (IV).—This was prepared by heating *m*-iodotoluene and methyl 1-bromo-2-naphthoate with copper bronze (Baddar and Gindy, *J.*, 1948, 1231). After hydrolysis and partial separation of the product, the acid was esterified with methanol and hydrogen chloride (Baddar and Gindy used diazomethane), and the ester distilled. The fraction boiling at 187—195°/4 mm. was hydrolysed and the 3'-methyl-1-phenylnaphthalene-2-carboxylic acid crystallised from aqueous ethanol.

Brucine Salt of 3'-Methyl-1-phenylnaphthalene-2-carboxylic Acid.—The acid (0·3000 g., 1 mol.) and anhydrous brucine (0·4506 g., 1 mol.) were dissolved together in boiling acetone (40 c.c.), and ether (80 c.c.) was added. The cooled solution deposited the *salt* (0·5517 g.), m. p. 198° (Found: C, 74·4; H, 6·25; N, 4·0. $C_{41}H_{40}O_6N_2$ requires C, 75·0; H, 6·1; N, 4·3%). The salt showed no mutarotation at 5° in chloroform solution, and on decomposition gave an inactive acid.

1 : 1'-*Dinaphthyl*-8 : 8'-*dicarboxylic Acid* (VI).—Methyl 8-bromo-1-naphthoate was prepared from 8-bromo-1-naphthoic acid (Rule, Pursell, and Brown, *J.*, 1934, 168) *via* the acid chloride. It had m. p. 35—37°. Rule and Barnett (*J.*, 1932, 175) give m. p. 33°. By heating this ester with copper bronze at 300° for ½ hr. and extracting the resulting mixture in a Soxhlet apparatus with acetone, *methyl* 1 : 1'-*dinaphthyl*-8 : 8'-*dicarboxylate* (50%), m. p. 155—159°, was obtained (Found: C, 77·8; H, 5·2. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%). Hydrolysis of the ester with solid potassium hydroxide gave 1 : 1'-dinaphthyl-8 : 8'-dicarboxylic acid, m. p. 300—304°. (Meisenheimer and Beisswenger, *loc. cit.*, used ethyl 8-chloro-1-naphthoate.)

Optical Resolution of 1 : 1'-*Dinaphthyl*-8 : 8'-*dicarboxylic Acid.*—This was carried out on lines similar to those described by Meisenheimer and Beisswenger (*loc. cit.*) and the racemisation of the active acids followed in 0·1N-sodium hydroxide at 20°. k for (−)-acid was: (1) 0·0043 min.$^{-1}$, (2) 0·0042 min.$^{-1}$. k for (+)-acid was: (1) 0·0040 min.$^{-1}$, (2) 0·0044 min.$^{-1}$, whence half-life is 165 min.

1-*Phenylnaphthalene-2'* : 8-*dicarboxylic Acid* (IX).—This was prepared by the general method described by Rule, Pursell, and Barnett, *J.*, 1935, 751.

First-order Asymmetric Transformations with Brucine: Acid–Base Ratio 1 : 1.—A chloroform solution (20 c.c.) containing acid (0·1000 g.) and anhydrous brucine (0·1347 g.) and 0·5 c.c. of ethyl alcohol was examined polarimetrically at 20° and showed mutarotation from α^{20}_{5461} −0·29° to +0·45°. In two separate experiments, k = 0·0012 and 0·0013 min.$^{-1}$, half-life = 550 min.

Acid–Base Ratio 1 : 2.—A chloroform solution (20 c.c.) containing acid (0·1000 g.), anhydrous brucine (0·2695 g.), and ethyl alcohol (0·5 c.c.) was examined polarimetrically at 20°. In two experiments the observed angle changed from −2·01° (−2·13°) to −1·40° (−1·47°). k = 0·0049 and 0·0049 min.$^{-1}$; half-life = 140 min.

Second-order Asymmetric Transformation.—The acid (0·5000 g., 1 mol.) and anhydrous brucine (0·6735 g., 1 mol.) were dissolved in 150 c.c. of benzene, and the solution was evaporated to 30 c.c. The *salt* obtained (0·9520 g., 75% of total solids) had m. p. 205°, $[\alpha]^{20}_{5461}$ +66° (*c*, 0·500 in $CHCl_3$) (Found: C, 72·4; H, 5·8; N, 4·0. $C_{41}H_{38}O_8N_2$ requires C, 71·7; H, 5·6; N, 4·1%). A solution of the salt (0·1000 g.) and 0·5 c.c. of ethyl alcohol in chloroform was made up to 20 c.c. and examined polarimetrically at 20°. k for equilibration in two separate experiments = 0·0015 and 0·0015 min.$^{-1}$, half-life = 460 min.

(+)-1-*Phenylnaphthalene-2'* : 8-*dicarboxylic Acid.*—The brucine salt was ground with dilute hydrochloric acid, and the liberated acid washed with hydrochloric acid and water and dried. The acid was examined polarimetrically in chloroform solution at 20°. (*a*) A solution (10 c.c.) containing 0·0500 g. of acid was shaken three times with dilute hydrochloric acid and once with water before being examined polarimetrically (1-dm. tube). The low observed angles render the value for k subject to a considerable experimental error. $k \sim 0{\cdot}0030$ min.$^{-1}$; half-life = 230 ± 40 min.

(*b*) A similar solution was examined without further washing (*i.e.*, the "B.P." chloroform contained the normal amount of alcohol). The first reading was made 2·5 min. after wetting of

the acid solvent and the first observed angle was $+0{\cdot}16°$ ($l = 1$). $k = 0{\cdot}0115$ min.$^{-1}$; half-life = 60 ± 8 min.

(*c*) 0·1000 g. of acid and 0·5 c.c. of ethyl alcohol were dissolved in chloroform and the volume made up to 20 c.c. The first reading (4·5 min. after wetting) was $+0{\cdot}35°$. $k = 0{\cdot}020$ min.$^{-1}$; half-life = 35 ± 2 min.

Absorption Spectra.—Spectra were determined in 96% ethanol ($1{\cdot}25 \times 10^{-5}$M-solutions) on a Unicam S.P. 500 Spectrophotometer.

We are grateful to Dr. G. H. Beaven for valuable discussions. We thank Imperial Chemical Industries Limited for a grant, the Department of Scientific and Industrial Research for a maintenance grant to one of us, and the Central Research Fund of the University for a grant for the purchase of a spectrophotometer.

BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, February 19th*, 1954.]

The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part VI. Solvolysis and the accompanying Rearrangement of* 1 : 1- *and of* 3 : 3-*Dimethylallyl Chloride.*

By P. B. D. DE LA MARE and C. A. VERNON.

[Reprint Order No. 5150.]

The kinetics of the solvolysis of 1 : 1- and of 3 : 3-dimethylallyl chloride have been examined in ethanol and in aqueous ethanol, both with and without added chloride or ethoxide ions. The products recoverable from partial reaction of the former compound in 75% ethanol in the presence of $^{36}Cl^-$ include 1 : 1-dimethylallyl [^{36}Cl]chloride and 3 : 3-dimethylallyl [^{36}Cl]chloride. Similarly, 1 : 1-dimethylallyl [^{36}Cl]chloride can be identified in the products of partial solvolysis of 3 : 3-dimethylallyl chloride in the presence of $^{36}Cl^-$. These results are interpreted as evidence that solvolysis of these compounds in aqueous alcohol is accompanied by both (*a*) intramolecular rearrangement (S_Ni'; "internal return") and (*b*) unimolecular rearrangement (S_N1').

IN Part IV (*J.*, 1953, 3555), the second-order reaction of 1 : 1-dimethylallyl chloride with sodium thiophenoxide in ethanol, giving 3 : 3-dimethylallyl phenyl sulphide, was interpreted as a bimolecular nucleophilic displacement with anionotropic rearrangement (S_N2'). The structure and reactions of 1 : 1-dimethylallyl chloride (cf. Ultée, *Rec. Trav. chim.*, 1949, **68**, 483) make it clear, however, that both this compound and its allylic isomer are favourably disposed to unimolecular (S_N1) reactions in which ionisation, giving a mesomeric carbonium ion, is the rate-determining step; rate-comparisons supporting this view were presented in Part V (Vernon, *J.*, 1954, 423).

Young, Winstein, and Goering (*J. Amer. Chem. Soc.*, 1951, **73**, 1958) examined in detail the solvolysis of 1 : 1- and of 3 : 3-dimethylallyl chloride in glacial acetic acid, and observed that solvolysis of the former chloride is accompanied by rearrangement to the latter. The rates of the rearrangement and of the solvolyses were unaffected by added chloride ions (0·024M). It was deduced that the rearrangement is essentially intramolecular, in that the migrating chlorine atoms do not become kinetically equivalent to the chloride ions of the environment. They concluded that the migration involved an incipient formation of an ion-pair which collapsed to give the isomeric chloride more rapidly than it reacted to give products of solvolysis.

The present results extend our knowledge of the reactions of these compounds in ethanol and aqueous ethanol and show that both S_N1' and S_Ni' rearrangements can occur in this system.

EXPERIMENTAL

Materials and methods. The methods described in Parts IV and V (*locc. cit.*) were used for the preparation of 1 : 1- and 3 : 3-dimethylallyl chloride; their refractive indices were checked

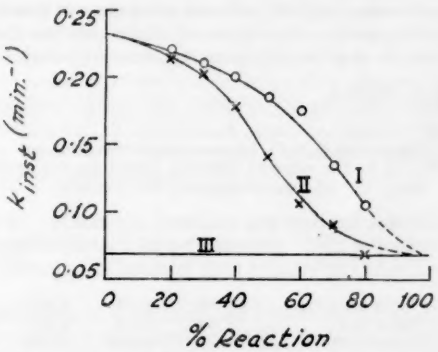
* Part V, *J.*, 1954, **423**.

before use. Solvents and general methods were as described in earlier parts. Sodium [^{36}Cl]chloride was supplied by the Atomic Energy Research Establishment, Harwell; it was distilled with dilute sulphuric acid, the first few ml. of distillate being rejected. The resulting solution of [^{36}Cl]hydrochloric acid was converted as required into lithium [^{36}Cl]chloride. Radioactivity was measured with a counter made by Twentieth Century Electronics Ltd. for counting of liquid samples, with standard amplifying and recording equipment.

*Kinetic measurements in 75% ethanol.** The following are the results for the solvolysis of 1 : 1-dimethylallyl chloride at 25·0°. At intervals, samples (5·0 ml.) were titrated in cooled ethanol with 0·0119N-sodium hydroxide, lacmoid being used as indicator. The stability of the end-points proved that the reaction was stopped instantaneously by this procedure. If the reaction is quenched with water, as was done by Hatch and Gerhardt (*J. Amer. Chem. Soc.*, 1949, **71**, 1677) and by Hatch and Journeay (*ibid.*, 1953, **75**, 3712), who used the method of Tamele, Ott, Marple, and Hearne (*Ind. Eng. Chem.*, 1941, **33**, 115) in studying the reactions of ethoxide ion in ethanol with 3 : 3-dimethallyl chloride and with 2 : 3 : 3-trimethylallyl chloride, further rapid hydrolysis results, as would be expected, and this is therefore an unsuitable method for these compounds.

Instantaneous rate coefficients ($k_{inst.}$) *for solvolyses in 75% ethanol at 25°.*

I = 1 : 1-Dimethylallyl chloride.
II = 1 : 1-Dimethylallyl chloride + lithium chloride (0·98M).
III = 3 : 3-Dimethylallyl chloride (mean k_1).



In the Figure are shown (circles) the instantaneous rate-coefficients, $k_{inst.} = (dx/dt)/(a - x)$, obtained by drawing, at intervals of 10% reaction, tangents to the curve of % reaction (x) against time (t). Similar results are also shown (crosses) for reaction under identical conditions, in the presence of added 0·98N-lithium chloride. The reactions are very fast, and it is difficult to estimate instantaneous rate-coefficients with precision, so that the observed scatter is not unexpected, but it is clear that the coefficients begin to decrease at an earlier point in the reaction when lithium chloride is present.

Time (min.)	0·00	0·67	1·35	2·05	2·60	3·58	5·05
Titre (ml.)	2·00	5·40	7·52	9·70	11·42	13·32	15·58
k_1* (min.$^{-1}$)	—	0·253	0·216	0·213	0·218	0·205	0·193
Time (min.)	6·80	8·87	10·87	14·05	17·13	21·13	∞
Titre (ml.)	17·51	18·80	19·79	20·70	21·49	21·90	23·80
k_1* (min.$^{-1}$)	0·183	0·166	0·156	0·137	0·131	0·116	—

* Values of k_1 are first-order rate-coefficients calculated by means of the usual formula $k_1 = 2{\cdot}303\ \{\log_{10}[a/(a - x)]\}/t$, where x is the amount of RCl which has reacted at time t. For a case such as this in which the rate-coefficients change with time, they represent a weighted average of the instantaneous rate-coefficients in the interval 0—t.

That the reaction is unimolecular was shown by examining the rate in the presence of added base. With 0·0371M-chloride, and 0·059M-potassium hydroxide, the extrapolated initial value of k_1 was 0·208 min.$^{-1}$, and this decreased to 0·12 min.$^{-1}$ at 90% reaction. The initial value of the rate coefficient and the decrease in rate as the reaction progresses are unaffected by the presence of alkali.

At 0·0°, similar experiments gave an initial value of $k_1 = 0{\cdot}0130$ min.$^{-1}$; from this value and the extrapolated $k_{inst.} = 0{\cdot}230$ min.$^{-1}$ for reaction at 25°, the energy of activation for the reaction is calculated to be 18·5 kcal./mole.

* The term y% ethanol refers to a solvent prepared by mixing y ml. of ethanol with (100 − y) ml. of water.

The following are results for the solvolysis of 3 : 3-dimethylallyl chloride at 25°. Samples (5·0 ml.) were pipetted into acetone and titrated with 0·0352N-sodium hydroxide, lacmoid being used as indicator.

Time (min.) ...	0·00	3·83	5·93	7·95	10·19	12·57	19·00	23·25	27·79	34·75	∞
Titre (ml.)	0·49	2·29	3·12	3·81	4·55	5·19	6·39	6·99	7·40	7·80	8·51
k_1 (min.$^{-1}$)	—	0·066	0·067	0·065	0·069	0·070	0·070	0·072	0·071	0·070	—

The reaction was followed over 91%, and the rate coefficients (mean, 0·069) do not fall. With added sodium hydroxide (0·0584N, 0·1050N), the mean rate coefficients were 0·071 and 0·066, respectively. At 0·0°, $k_1 = 0·00338$ min.$^{-1}$, whence the activation energy is 19·4 kcal./mole.

Products of solvolysis in 75% ethanol. It is generally difficult to recover unchanged organic chloride from the product of the partial reaction of an allylic chloride with aqueous ethanol, since the products (ethers and alcohols) have boiling points near those of the chlorides, and azeotropes are often formed between the reactants. In the following experiment (*A*), 1 : 1-dimethylallyl chloride (26 g.; n_D^{25} 1·4175) was added to 700 ml. of a solution in 75% ethanol of 0·706N-lithium [^{36}Cl]chloride. After 4·8 min. at 25° the mixture was added to cold pentane, and was washed rapidly with ice-water several times. The pentane extract was dried (Na_2SO_4), and fractionated. After removal of the pentane the following fractions, which were analysed for chloride and for radioactivity, were collected:

B. p./120 mm.	40—42°	42—56°	56—61°	61—62°	62—65°
Wt.	0·9	2·3	2·2	1·4	1·1
n_D^{25}	1·4055	1·4082	1·4286	1·4400	1·4390
%-Purity (as C_5H_9Cl, by quantitative hydrolysis)	43·6	32·5	61·4	80·3	74·7
^{36}Cl (% in the organic chloride, based on the activity of inorg. Cl^- at time of stopping the reaction)	37	40	61	63	64

The last fraction was analysed kinetically. A sample (1·026 g.) was added to 100 ml. of 75% ethanol at 25°. Samples (5·0 ml.) were removed at intervals and titrated with 0·0169N-sodium hydroxide in ethanol with lacmoid as indicator:

Time (min.)	0·00	2·00	4·00	8·20	10·66	16·50	20·35	∞
Titre (ml.)	1·69	4·12	6·31	10·20	12·02	15·20	16·80	21·72
k_1 (min.$^{-1}$)	—	0·065	0·066	0·067	0·068	0·068	0·069	—

The mean velocity coefficient agrees well with that for 3 : 3-dimethylallyl chloride.

To check the method of recovery the following experiment (*B*) was performed. 1 : 1-Dimethylallyl chloride (25 g.; n_D^{25} 1·4170) was added to 750 ml. of a 75% ethanolic solution of 0·675N-lithium [^{36}Cl]chloride. The reaction was stopped within 1 min. and the material was worked up as before giving the following fractions:

B. p./124 mm.	34—36°	36—58°	58—60°	residues *
Wt. (g.)	4·7	0·7	1·1	0·3
n_D^{25}	1·4158	1·4260	1·4411	—
%-Purity (as C_5H_9Cl, by quantitative hydrolysis)	86	76	81	—
^{36}Cl (% in the organic chloride, based on the activity of the original Cl^-)	3	13	20	—

* From column and still-pot, by titration of the chloride produced on hydrolysis; this figure is recorded to show that almost all of the chloride had been distilled.

Very much less rearranged chloride, containing a very much smaller proportion of ^{36}Cl, was produced in experiment *B* than in *A*.

The following are the results of an experiment (*C*), in which 3 : 3-dimethylallyl chloride (37 g.) was allowed to react for 5 min. at 25° with 900 ml. of a 75% ethanolic solution of 0·584N-lithium [^{36}Cl]chloride. From the product there was obtained an initial fraction (0·75 g.), b. p. 40—44°/124 mm., containing 34% of C_5H_9Cl (by quantitative hydrolysis), and 40% of ^{36}Cl in the organic chloride (based on the activity of the Cl^- in the solution when the reaction was stopped). A final fraction of unchanged 3 : 3-dimethylallyl chloride, b. p. 63°/124 mm., n_D^{25} 1·4472, had a corresponding ^{36}Cl activity of 20%. The initial fraction was analysed kinetically by adding a sample (0·706 g.) to 50 ml. of 75% ethanol at 25°. Samples (5·0 ml.) were titrated with 0·0169N-alkali in chilled ethanol, with lacmoid as indicator:

Time (min.)	0·00	0·80	1·62	2·73	4·12	6·25	∞
Titre (ml.)	1·29	2·95	4·50	6·14	7·60	9·05	13·40
x (% reaction)	10	22	34	46	57	68	100
k_1 (min.$^{-1}$)	—	0·184	0·190	0·187	0·179	0·164	—

The accordance between this result and that recorded above for 1 : 1-dimethylallyl chloride shows that there has been isolated a small quantity of this product of rearrangement, probably contaminated with 1 : 1- and 3 : 3-dimethylallyl ethyl ether.

Kinetics of solvolysis in ethanol. The reaction of 1 : 1-dimethylallyl chloride in ethanol at 44·6° has $k_1 = 0{\cdot}0110$ min.$^{-1}$. With addition of 0·097N-sodium ethoxide, k_1 is 0·0124 min.$^{-1}$. The following are the results for the reaction with addition of 0·053N-sodium ethoxide. Portions (5·53 ml.) were added to 100 ml. of chilled ethanol containing 5·00 ml. of 0·0871N-acid, and were back-titrated with 0·0110N-sodium hydroxide.

Time (min.)	0·00	12·00	18·00	31·50	46·00	68·00	95·00	153·5	162·0	∞
Titre (ml.) ...	13·32	14·82	15·55	16·78	18·19	19·44	20·79	22·40	22·70	24·35
k_1 (min.$^{-1}$) ...	—	0·0121	0·0125	0·0119	0·0126	0·0119	0·0119	0·0113	0·0118	—

These details show that k_1 in this solvent is sensibly constant over the whole course of the reaction. With added M-lithium chloride, k_1(0·0143 min.$^{-1}$) is constant over at least 50% reaction. 3 : 3-Dimethylallyl chloride reacts more slowly; at 60·4° $k_1 = 0{\cdot}0192$, and at 35°, $k_1 = 0{\cdot}00132$ min.$^{-1}$, whence $E = 22{\cdot}2$ kcal./mole. In contrast with that of its allylic isomer, the reaction of this compound is accelerated by sodium ethoxide, showing the incursion of a bimolecular substitution, which becomes the dominant reaction ($k_2 = 0{\cdot}064$ l. mole^{-1} min.$^{-1}$ at 35·0°) when the concentration of ethoxide ion becomes sufficiently large (*e.g.*, >0·1M).

Products of solvolysis in ethanol. 3 : 3-Dimethylallyl chloride was solvolysed in ethanol at 60—70°, the solution being stirred and kept neutral during the reaction by titration with alcoholic sodium ethoxide with lacmoid as indicator.* The product was extracted with *n*-pentane, and the extracts were washed with water and fractionated, a 3′ helix-packed, jacketed column being used. The following fractions were collected :

Wt. (g.) ...	3·31	1·31	1·90	1·87	3·08	1·86	2·00	1·26	3·44	0·47
B. p.	40—90°	90—94°	94—96°	96—98°	98—105°	105—120°	120—126°	126°	126°	residues
n_D^{25}	1·3762	1·3938	1·3972	1·3989	1·3993	1·4045	1·4142	1·4160	1·4162	1·4278

It being assumed that the fractions are binary mixtures of *n*-pentane (n_D^{25} 1·3550) and 1 : 1-dimethylallyl ethyl ether (n_D^{25} 1·3991), or of the latter and 3 : 3-dimethylallyl ethyl ether (n_D^{25} 1·4162), it can be estimated that the product (75% yield, the residues being neglected) contained 60% of 1 : 1-dimethylallyl ethyl ether and 40% of 3 : 3-dimethylallyl ethyl ether. A similar experiment, with 1 : 1-dimethylallyl chloride, gave a mixture containing 70% of 1 : 1-dimethylallyl ethyl ether and 30% of 3 : 3-dimethylallyl ethyl ether. We consider the difference between these proportions to be greater than the experimental error which we consider to be ±3%.

Although the corresponding methyl ethers have been described by Ultée (*Rec. Trav. chim.*, 1949, **68**, 352), and 3 : 3-dimethylallyl ethyl ether has been characterised by Claisen, Kremers, Roth, and Tietze (*J. pr. Chem.*, 1922, **105**, 80), 1 : 1-*dimethylallyl ethyl ether* has not been reported previously. Refractionation of bulked fractions from the above two solvolyses gave a product of constant b. p. 98—99° and n_D^{25} 1·3991, having a camphoraceous odour (Found : C, 73·8; H, 12·4. $C_7H_{14}O$ requires C, 73·7; H, 12·3%).

Kinetics of solvolysis in 50% ethanol. In 50% ethanol at 0°, 3 : 3-dimethylallyl chloride solvolyses rapidly (k_1, 0·093 min.$^{-1}$). The corresponding reaction of 1 : 1-dimethylallyl chloride is extremely rapid, and its small solubility makes it difficult to obtain a point at an early stage in the reaction. The rate coefficient is initially probably rather greater than 0·5 min.$^{-1}$, and drops to 0·17 min.$^{-1}$ at 90% reaction, showing that rearrangement accompanies the solvolysis in this solvent.

Search for products of elimination. The most likely product of elimination from either of these chlorides is isoprene, which has an intense absorption maximum in the neighbourhood of 2200 Å ($\varepsilon = 19{,}800$); 1 : 1-dimethylallyl chloride has no appreciable absorption in this region, but 3 : 3-dimethylallyl chloride has some absorption (in ethanol : $\varepsilon = 3000$ at 2150 Å, $\varepsilon = 2300$ at 2200 Å). This absorption, which was measured with a Unicam ultra-violet spectrophotometer, Model SP 500, disappears when the compound solvolyses in ethanol, and hence the ethers produced by solvolysis have little or no absorption in this region. Reaction

* It is estimated that the solution never contained more than M/8000-OEt^-, whence it is estimated that a bimolecular reaction with ethoxide contributed no more than 1% to the total reaction. A bimolecular reaction with ethanol molecules would have contributed less than 2%, if a ratio of 10^5 is assumed for the bimolecular rate coefficients for OEt^- and EtOH.

mixtures were analysed for isoprene by measuring the absorption at 2200 Å, with the following results:

Compound	Solvent	[Alkali]	Temp.	Isoprene
3 : 3-Dimethylallyl chloride	75% Ethanol	—	25·1°	⩾2·0%
1 : 1-Dimethylallyl chloride	75% Ethanol	—	25·1	⩾3·7
1 : 1-Dimethylallyl chloride	Ethanol	0·06M	44·6	⩾1·7

The conclusion is that significant amounts of products of elimination are not formed in the S_N1 reactions of these compounds.

Discussion

Both 1 : 1- and 3 : 3-dimethylallyl chloride undergo unimolecular solvolysis in aqueous ethanol, the reactions not being accelerated by added base. In ethanol the solvolyses themselves are still unimolecular, but the reaction of 3 : 3-dimethylallyl chloride becomes bimolecular on addition of sodium ethoxide, though it requires about 0·1M-ethoxide ions to make the latter mode of reaction dominant. The following Table summarises the effect of solvent on the rate coefficients.

Rates (k_1, *min.*$^{-1}$) *of Unimolecular Solvolyses.*

Compound	Temp.	k_1 in ethanol	k_1 in 75% ethanol	k_1 in 50% ethanol
1 : 1-Dimethylallyl chloride	0·0°	—	0·013	*ca.* 0·5
	25·1	0·0011	0·23	—
3 : 3-Dimethylallyl chloride	0·0	—	0·0034	0·098
	25·1	0·00039 *	0·069	—

* Extrapolated from measurements at 60° and 35°.

As expected for a reaction whose rate is determined by an ionisation, the velocity is very much greater in aqueous ethanol than in pure ethanol. As is generally characteristic of anionotropically related halides, the more stable thermodynamically of the two isomers is the less reactive.

In ethanol the reaction is not significantly complicated by rearrangement, and for both isomers the solvolysis is substantially unimolecular. Both isomers give a mixture of ethers, in which the tertiary isomer predominates, and the proportions of tertiary and primary compound are to a first approximation the same, as would be expected if a mesomeric carbonium ion were formed from each isomer and became completely free from the departing anion before reacting with the solvent. Several cases of approximations to this behaviour have been recorded (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; Roberts, Young, and Winstein, *J. Amer. Chem. Soc.*, 1942, **64**, 2157; Catchpole, Hughes, and Ingold, *J.*, 1948, 8). Generally, as in the present example, there is a small difference in the observed proportions in the direction expected if the reaction of the 3-substituted halide had a small bimolecular component. If our estimates of the bimolecular reaction between ethanol and 3 : 3-dimethylallyl chloride are correct, then in the present example the discrepancy is real, requiring another interpretation; but in view of the uncertainty in this calculation, the matter remains open. The present experiments supplement those of Ultée, who showed (*locc. cit.*) that both chlorides in aqueous sodium carbonate give similar mixtures of alcohols, and that methanolysis of the tertiary chloride gives a mixture of tertiary and primary methyl ethers.

The Chloride-catalysed Rearrangement.—Our main concern has been to examine the rearrangement of 1 : 1-dimethylallyl chloride in 75% ethanol, and to discover the rôle, if any, played by added chloride ions in this solvent. The kinetic results illustrated in the Figure show that in the course of solvolysis of 1 : 1-dimethylallyl chloride the value of the instantaneous rate coefficient falls to that corresponding to the rearranged isomer. This decrease is more rapid in the presence of M-lithium chloride solution, indicating that the more slowly reacting 3 : 3-isomer is produced more rapidly in the presence of chloride ions. Young, Winstein, and Goering (*loc. cit.*) found no such increased rate of decrease for the same reaction in acetic acid, but their test involved the addition of a very much smaller concentration of chloride ions.

The latter workers showed that the rate of the rearrangement, k_i, is given by the formula $k_i = 2{\cdot}303\{\log_{10}[a/(a - x)F]\}/t - k_T$, where F is the value of the fraction

$(k_{inst.} - k_P)/(k_T - k_P)$, $k_{inst.}$ having reference to a time t, and k_P and k_T being the initial first-order rate coefficients for the solvolyses of the 3 : 3- and 1 : 1-isomers, respectively. This formula is valid for an intramolecular rearrangement, or for a rearrangement dependent on halide ions provided that the concentration of these does not change much during the reaction. On these assumptions, and k_P and k_T being taken as 0·071 min.$^{-1}$ and 0·234 min.$^{-1}$ respectively (these values being consistent with the results illustrated in the Figure), $k_i = 0{\cdot}081$ min.$^{-1}$ in the absence of lithium chloride, and 0·162 in the presence of 0·98N-lithium chloride; the assumption of these values gives the measured course of the reaction to a good approximation which is certainly within the experimental error.

Consistently with these kinetic results, it has been shown that 3 : 3-dimethylallyl chloride can be isolated from the product of solvolysis of 1 : 1-dimethylallyl chloride in 75% ethanol. Thus in Experiment *A*, the last two fractions of recovered halide consisted largely of 3 : 3-dimethylallyl chloride, as shown by the boiling points, refractive indices, and kinetic analysis. The ratio $^{36}Cl : Cl^-$ was shown to be relatively low in the early fractions recovered which would have been expected to contain much inactive starting material in this experiment. The last three fractions, however, gave a higher, nearly constant value, which was about 63% of the corresponding value for the free chloride ion in the solution. This indicates that only a part of the 3 : 3-dimethylallyl chloride was obtained by intervention of external chloride ions; the remainder must have come from the starting material by intramolecular rearrangement.

In considering possible ways in which the rearranged material containing ^{36}Cl could have been formed, the possibility must be excluded that isomerisation occurred during the isolation of the product. In Experiment *B*, a replica of Experiment *A* except that the reaction was stopped much earlier, very much less 3 : 3-dimethylallyl chloride was isolated, and the material that was obtained contained a much smaller proportion of ^{36}Cl. This indicates that the rearranged product was not an artifact.

Another possible route to the rearranged product is by bimolecular attack of chloride ions on 1 : 1-dimethylallyl chloride, accompanied by synchronous rearrangement (the S_N2' reaction), but this can also be excluded, in our opinion, on the grounds that the bimolecular S_N2' reaction of this compound with chloride ions could not possibly be as fast as the observed reaction in such an ionising solvent. Thus, chloride ions do not normally compete successfully with ethoxide ions as nucleophilic reagents; and we know from the ineffectiveness of ethoxide ions in accelerating the solvolysis (cf. Part IV, *loc. cit.*) that even these ions cannot compete in a bimolecular process with the S_N1 reaction of this compound; to observe the S_N2' reaction a much more powerfully nucleophilic reagent, such as the thiophenoxide ion, must be used. These arguments apply to ethanol as solvent and more especially to the more ionising conditions of our experiments, since bimolecular reactions of ions with neutral molecules are in general little facilitated by increase in the ionising power of the solvent. Our results show that the chloride-catalysed rearrangement is very powerfully accelerated by the addition of water to the solvent. This is in agreement with, and supports, the view that this reaction is dependent on a S_N1' rate-determining ionisation.

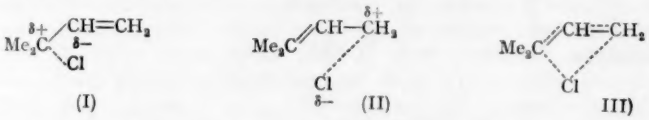
The product of solvolysis of 3 : 3-dimethylallyl chloride in the presence of ^{36}Cl in 75% ethanol has also been examined (Experiment *C*). Since in this case the product of the rearrangement is solvolysed more rapidly than the starting material, its isolation is much more difficult. There was, however, obtained from the reaction a low-boiling sample, containing, from its behaviour on kinetic analysis, 1 : 1-dimethylallyl chloride as essentially the only organic chloride. This material contained about twice as much ^{36}Cl, per unit of organic chloride present, as the later fractions which, as expected, were nearly pure 3 : 3-dimethylallyl chloride. Less than half of the rearranged material can therefore have been derived from the starting material, which at the beginning of the reaction was inactive and at the end of the reaction was only slightly active. The rearranged material must have been formed mainly by a S_N1' halide-catalysed rearrangement.

Our observations show that two mechanisms are concerned in the interconversion of 1 : 1- and 3 : 3-dimethylallyl chloride in aqueous ethanol. One is intramolecular and involves no exchange with radioactive chloride ions present in the solution, and the other,

which increases in importance as the chloride-ion concentration is increased, involves exchange with radioactive chloride ions, and leads to the introduction of ^{36}Cl into both rearranged and unrearranged products. It is considered that this exchange occurs after the rate-determining stage of the reaction. The process is formulated as follows (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 8):

$$CH_2{:}CH{\cdot}CMe_2Cl \underset{+Cl^-}{\overset{-Cl^-}{\rightleftharpoons}} \overset{+}{CH_2{=}CH{=}CMe_2} \underset{-Cl^-}{\overset{+Cl^-}{\rightleftharpoons}} Cl{\cdot}CH_2{\cdot}CH{:}CMe_2 \quad . \; . \; . \quad S_Ni'$$

The intramolecular rearrangement can be formulated as an S_Ni' reaction, involving a transition state of the type indicated in the canonical structures I, II, III:



(I) (II) III)

To accommodate the powerful influence of increased ionising power of the solvent on the rate of reaction, solvation of the incipient carbonium centre must not be greatly diminished by distribution of the charge over the anionotropic system: in this example this assumption does not seem unreasonable, seeing that there is considerable congestion at the 1-carbon atom where solvation forces must in any case be considerably reduced both by steric effects and by the charge-distributing effect of C–H hyperconjugation. Young, Winstein, and Goering (*loc. cit.*) have preferred to consider that the reaction involves an ion-pair which is formed in the rate-determining reaction, and subsequently either collapses to give rearranged chloride (internal return) or dissociates to give free ions.

We are indebted to Professors E. D. Hughes, D.Sc., F.R.S., and C. K. Ingold, D.Sc., F.R.S., for their interest and encouragement. Analyses are by Mr. A. V. Winter of this Department.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, February 24th*, 1954.]

The Kinetics of Chlorohydrin Formation. Part V. The Reaction between Hypochlorous Acid and Crotonic Acid in Buffered Solutions at 25° and 35°.*

By D. A. CRAW.

[Reprint Order No. 4823.]

The study of the reaction in aqueous solution between hypochlorous acid and crotonic acid buffered by sodium crotonate to pH 4·73 was continued. The velocity equation for the reaction at 35° ± 0·01° conformed to the general equation derived by Craw and Israel (*J.*, 1952, 550) for the reaction at 25° ± 0·01°, *viz.*,

$$v = k_2^{I}[HOCl]\{[R{\cdot}CO_2H] + [R{\cdot}CO_2^-]\} + \{k_2^{II} + k_3^{II}[R{\cdot}CO_2H]\}[HOCl]^2$$

where R = $CH_3{\cdot}CH{:}CH{\cdot}$. The activation energies of the individual reactions occurring between these compounds were calculated from the ratios of the specific rate constants at 25° and 35°. The effect of pH on the rate of addition of hypochlorous acid to crotonic acid was investigated at 25° and 35° and reasons have been advanced for the behaviour exhibited.

IN view of the satisfactory equation developed for the addition of hypochlorous acid to crotonic acid at 25° (Craw and Israel, *J.*, 1952, 550) this reaction was studied in an analogous manner at 35°. If it could be shown that the kinetics of the reaction at 35° could be expressed by an equation of the form

$$v = k_2^{I}[HOCl]\{[R{\cdot}CO_2H] + [R{\cdot}CO_2^-]\} + \{k_2^{II} + k_3^{II}[R{\cdot}CO_2H]\}[HOCl]^2 \quad . \quad (1)$$

* Part IV, *J.*, 1952, 2327.

derived for the reaction at 25°, then the specific rate constants for the individual terms could be compared with a view to calculating the activation energies for these stages in this temperature interval.

The effect of pH on the rate of addition of hypochlorous acid to olefins has been noted previously. Israel, Martin, and Soper (*J.*, 1950, 1282) found that in the rate equation developed for the addition of hypochlorous acid to allyl alcohol,

$$v = k_2^{I}[HOCl][C_3H_5{\cdot}OH] + k_2^{II}[HOCl]^2 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

k_2^{I} increased and k_2^{II} decreased with increasing pH. More recently, Shilov, Kupinskaya, and Yasnikov (*Doklady Akad. Nauk S.S.S.R.*, 1951, **81**, 435) found that the rate of addition of hypochlorous acid to trimethylallylammonium perchlorate decreased with increasing pH, becoming zero at pH 8·1.

In kinetic equations of the type so far established for crotonic acid, it is difficult to forecast the overall effect of a pH change. A pH change that increases the magnitude of one term in the equation may cause another to decrease while the overall result involves the sum of all the terms.

Experimental and Results

Materials.—Crotonic acid, from B.D.H., was recrystallised from light petroleum; it had m. p. 72°. Hypochlorous acid was prepared by a variation of the method used by Israel *et al.* (*loc. cit.*). The crude hypochlorous acid solution, distilled with yellow mercuric oxide in an all-glass apparatus in the dark, had b. p. 20—25°/15—20 mm. Solutions ranging in strength from 0·2—0·9M were obtained, but were diluted to 0·1M before storage in the dark at 4°. This stock solution kept well and was diluted as required.

The initial velocity, v_0, was plotted against the total olefin concentration for constant hypochlorous acid concentration for ten of the twelve series studied and these graphs indicated a linear relation of the form,

$$v_0 = k([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0) + v'_{res} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where both k and v'_{res} are functions of the hypochlorous acid concentration. From Pitzer's equation for the variation of the dissociation constant of weak acids with temperature (*J. Amer. Chem. Soc.*, 1937, **59**, 2365) and the known value of the dissociation constant at 25°, *viz.*, $2{\cdot}03 \times 10^{-5}$, the dissociation constant at 35° was calculated as $2{\cdot}05 \times 10^{-5}$. The value of pK_a remained unchanged at 4·69 so that buffer solutions of the same composition were used in the experiments at both 25° and 35°. Therefore, as previously (*loc. cit.*), the ratio $[R{\cdot}CO_2^-]_0/[R{\cdot}CO_2H]_0$ where R = $CH_3{\cdot}CH{:}CH{\cdot}$ was kept constant and equal to 1·096, and equation (3) can be modified to equation (4),

$$v_0 = k'[R{\cdot}CO_2H]_0 + v'_{res} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The effect of a large excess of one reactant was studied in the K′ and L′ series, but these results were not used in the determination of the velocity equation. k' and v'_{res} were calculated by the method of least squares for each of the ten series A′—J′ (Table 1), and their variation with the concentration of hypochlorous acid was examined graphically. Results showed that k' and v'_{res} vary according to equations (5) and (6) respectively and the method of least squares was used to calculate the lines of best fit to be

$$k'/[HOCl]_0 = 2{\cdot}096k_2^{I} + k_3^{II}[HOCl]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and

$$v'_{res} = k_2^{II}[HOCl]_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $k_2^{I} = 7{\cdot}1$ l. mole^{-1} min.$^{-1}$, $k_3^{II} = 4{\cdot}0 \times 10^3$ l.^{2} mole^{-2} min.$^{-1}$, and $k_2^{II} = 6{\cdot}9$ l. mole^{-1} min.$^{-1}$.

Substituting equations (5) and (6) in equation (4), we obtain the complete velocity equation,

$$v_0 = 7{\cdot}1[HOCl]_0([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0) + 4{\cdot}0 \times 10^3[HOCl]_0^2[R{\cdot}CO_2H]_0 + 6{\cdot}9[HOCl]_0^2 \quad (7)$$

This equation is represented in general form by equation (1). That equation (7) gives a reasonably accurate interpretation of the course of the reaction is confirmed since values of v_0 calculated by using it are in good agreement with the observed values (see Table 1).

That this generalisation of initial velocity data is valid was shown by integrating equation (7) to give the variation of the concentration of hypochlorous acid with time. If the time for a

TABLE 1. Initial pH = 4·73. Temperature = 35° ± 0·01°.

Run no.	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	v_0 (moles l.$^{-1}$ min.$^{-1}$) $\times 10^5$ obs.	calc.	Run no.	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	v_0 (moles l.$^{-1}$ min.$^{-1}$) $\times 10^5$ obs.	calc.
A′1	1·54	2·0	4·3	4·7	G′1	3·48	2·0	17·7	17·9
A′2	1·54	4·0	7·5	7·8	G′2	3·45	4·0	27·5	27·1
A′3	1·53	6·0	10·5	10·8	G′3	3·45	6·0	37·6	36·6
A′4	1·53	8·0	13·8	13·9	G′4	3·45	8·0	47·6	46·1
A′5	1·53	10·0	16·8	16·5	G′5	3·45	10·0	56·4	55·4
B′1	1·96	2·0	6·7	6·9	H′1	3·98	2·0	22·3	22·6
B′2	1·96	4·0	10·9	11·2	H′2	3·96	4·0	34·4	34·1
B′3	1·95	6·0	14·7	15·3	H′3	3·94	6·0	45·6	45·3
B′4	1·95	8·0	18·9	19·6	H′4	3·94	8·0	57·0	56·9
B′5	1·95	12·0	26·9	28·0	H′5	3·94	10·0	67·7	68·4
C′1	2·44	2·0	9·8	9·9	I′1	4·44	2·0	28·9	27·5
C′2	2·44	4·0	16·2	15·6	I′2	4·45	4·0	43·6	41·5
C′3	2·44	6·0	22·1	21·3	I′3	4·42	6·0	55·7	54·8
C′4	2·43	8·0	27·5	26·9	I′4	4·42	8·0	70·7	68·6
C′5	2·42	10·0	32·7	32·6	I′5	4·39	10·0	79·2	81·3
D′1	2·84	2·0	12·7	12·7	J′1	4·64	2·0	26·7	29·7
D′2	2·81	4·0	19·5	19·5	J′2	4·64	4·0	43·7	44·5
D′3	2·81	6·0	26·5	26·6	J′3	4·64	6·0	59·3	59·3
D′4	2·81	8·0	33·9	33·6	J′4	4·63	8·0	74·6	74·0
D′5	2·81	10·0	40·7	40·5	J′5	4·63	10·0	88·4	88·8
E′1	3·04	2·0	13·8	14·2	K′1	10·00	2·0	84·1	121·3
E′2	3·03	4·0	21·7	22·0	K′2	10·07	4·0	169·5	176·1
E′3	3·03	6·0	30·3	29·9	K′3	10·08	6·0	252·7	229·6
E′4	3·03	8·0	38·2	37·6					
E′5	3·03	10·0	47·7	45·6	L′1	2·42	12·0	38·8	38·2
					L′2	2·42	16·0	52·6	49·6
F′1	3·46	2·0	17·5	17·8	L′3	2·40	20·0	66·0	60·2
F′2	3·45	4·0	27·6	27·1					
F′3	3·45	6·0	37·4	36·6					
F′4	3·44	8·0	45·9	45·8					
F′5	3·41	10·0	53·8	54·5					

TABLE 2. Temperature = 25° ± 0·01°.

Series no.	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	$[R{\cdot}CO_2H]_0$ $\times 10^3$	v_0 $\times 10^5$	pH $t = 0$	Series no.	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	$[R{\cdot}CO_2H]_0$ $\times 10^3$	v_0 $\times 10^5$	pH $t = 0$
A	3·14	2·0	1·50	7·5	4·21	E	3·10	8·0	6·00	22·3	4·21
	3·13	2·0	1·33	8·2	4·39		3·11	8·0	5·33	24·3	4·39
	3·14	2·0	1·00	9·6	4·69		3·09	8·0	4·00	24·0	4·69
	3·13	2·0	0·67	10·2	4·99		3·09	8·0	2·67	24·1	4·99
	3·13	2·0	0·50	10·7	5·17		3·09	8·0	2·00	23·8	5·17
B	3·11	4·0	3·00	12·5	4·21	F	3·24	8·0	6·00	21·4	4·21
	3·11	4·0	2·67	13·5	4·39		3·24	8·0	5·33	22·8	4·39
	3·10	4·0	2·00	14·4	4·69		3·24	8·0	4·00	24·5	4·69
	3·10	4·0	1·33	15·2	4·99		3·22	8·0	2·67	24·9	4·99
	3·11	4·0	1·00	15·7	5·17		3·22	8·0	2·00	25·0	5·17
C	3·05	6·0	4·50	17·0	4·21	G	3·07	10·0	7·50	27·0	4·21
	3·05	6·0	4·00	18·2	4·39		3·07	10·0	6·67	28·0	4·39
	3·04	6·0	3·00	18·7	4·69		3·06	10·0	5·00	28·2	4·69
	3·04	6·0	2·00	18·7	4·99		3·06	10·0	3·33	27·8	4·99
	3·05	6·0	1·50	19·4	5·17		3·07	10·0	2·50	27·6	5·17
D	3·08	8·0	6·00	21·5	4·21	H	2·98	10·0	7·50	21·7	4·21
	3·07	8·0	5·33	21·7	4·39		2·97	10·0	6·67	23·6	4·39
	3·07	8·0	4·00	23·2	4·69		2·97	10·0	5·00	25·5	4·69
	3·07	8·0	2·67	23·5	4·99		2·96	10·0	3·33	25·0	4·99
	3·07	8·0	2·00	23·7	5·17		2·96	10·0	2·50	25·0	5·17

certain percentage decrease in the concentration of hypochlorous acid as obtained from this integration compares favourably with the time for the same percentage decrease evaluated from the experimental (log titre)–time curves, then it can be assumed that equation (7) for the initial velocity is representative of the velocity at any stage of the reaction. Calculations for 10 and 20% decreases in the concentration of hypochlorous acid showed satisfactory agreement between the observed and the calculated values, *e.g.*, for H'5, $t_{1/10} = 0{\cdot}6$ min. (obs.), 0·6 min. (calc.); $t_{1/5} = 1{\cdot}3$ min. (obs.), 1·4 min. (calc.).

To investigate the effect of a variation in pH on the rate of reaction, mixed crotonic acid–sodium crotonate buffers were prepared in which the ratio $[R{\cdot}CO_2^-]_0/[R{\cdot}CO_2H]_0$ was equal to 1 : 3, 1 : 2, 1 : 1, 2 : 1, 3 : 1, corresponding to theoretical pH values of 4·21, 4·39, 4·69, 4·99, and 5·17 respectively.

The results obtained are listed in Tables 2 and 3 for data at 25° and 35° respectively.

TABLE 3. Temperature = 35° ± 0·01°.

$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	$[R{\cdot}CO_2H]_0$ $\times 10^3$	v_0 $\times 10^5$	pH $t = 0$	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	$[R{\cdot}CO_2H]_0$ $\times 10^3$	v_0 $\times 10^5$	pH $t = 0$
2·43	4·0	3·00	13·9	4·21	2·42	8·0	6·00	25·3	4·21
2·43	4·0	2·67	14·9	4·39	2·40	8·0	5·33	25·9	4·39
2·43	4·0	2·00	15·7	4·69	2·40	8·0	4·00	26·6	4·69
2·43	4·0	1·33	16·6	4·99	2·40	8·0	2·67	26·4	4·99
2·43	4·0	1·00	17·0	5·17	2·40	8·0	2·00	26·0	5·17

As seen in Table 2, the initial hypochlorous acid concentration was kept almost constant while the total olefin concentration was varied from 0·002 to 0·010M. The olefin concentration had a marked effect on the nature of the variation of velocity with pH. For low concentrations of crotonic acid plus sodium crotonate, the velocity increased steadily with pH throughout the range investigated, *e.g.*, series A, B, C. At higher concentrations of olefin, *e.g.*, series D, E, F, the increase in velocity with pH was not marked in the higher pH range 4·69—5·17, while in the G and H series the velocity reached its maximum value at a pH between 4·6 and 4·7.

DISCUSSION

The significance of the rate constants of equation (1) has been discussed previously (*loc. cit.*), but in view of more recent work the following information may be added.

The complex first term of equation (1) possibly includes a term for the rate of formation of crotonyl hypochlorite from crotonic acid and hypochlorous acid. That the formation of these acyl hypochlorites is due to the undissociated carboxylic acid and not to the carboxylate ion has been demonstrated recently by Shilov and Kupinskaya (*Doklady Akad. Nauk S.S.S.R.*, 1951, **81**, 621) who found that the catalytic effect of carboxylic acid and hypochlorous acid mixtures disappeared at a pH about 7·5 where the amount of free hypochlorous acid was still high, but where the amount of free carboxylic acid became insignificant.

The term, $k_3^{II}[HOCl]^2[R{\cdot}CO_2H]$, has been interpreted as the formation of chlorine monoxide from hypochlorous acid under the catalytic influence of undissociated crotonic acid. This, however, cannot be the only reason for the occurrence of this term in the rate equation. As will be shown in later papers, this term does not appear in the corresponding rate equations for tiglic and ββ-dimethylacrylic acid even though these acids are of approximately the same strength as crotonic acid.

The variation of the rate constants with temperature is summarised in Table 4.

TABLE 4.

	k_2^I	k_2^{II}	k_3^{II}
25°	$4{\cdot}5_1$	$4{\cdot}0_1$	$2{\cdot}0_6 \times 10^3$
35°	$7{\cdot}1_4$	$6{\cdot}8_9$	$4{\cdot}0_0 \times 10^3$
$k_{35°}/k_{25°}$	1·58	1·72	1·94
ΔE (kcal./mole^{-1})	8·38	9·87	12·10

$k_{35°}/k_{25°}$ represents the ratio of the rate constants for 35° and 25° respectively, and ΔE is the activation energy calculated by using the Arrhenius equation and assuming that the probability factor of the non-exponential coefficient in this equation remains independent of the temperature in this interval.

We will now review the effects of pH on the reaction velocity and in order to explain these results it is important to examine the effect of a pH change in relation to equation (1). Since the variation of pH was studied for series of constant initial hypochlorous acid concentration, equation (1) may be modified, so that

$$v = k_a([R{\cdot}CO_2H] + [R{\cdot}CO_2^-]) + k_b + k_c[R{\cdot}CO_2H] \quad . \quad . \quad . \quad . \quad (8)$$

Again since in any one series in Table 2 the value of $([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ is constant, the variation of velocity with pH is given by :

$$\partial v/\partial \mathrm{pH} = ([R{\cdot}CO_2H] + [R{\cdot}CO_2^-])\partial k_a/\partial \mathrm{pH} + \partial k_b/\partial \mathrm{pH} + [R{\cdot}CO_2H]\partial k_c/\partial \mathrm{pH} + k_c \,.\, \partial[R{\cdot}CO_2H]/\partial \mathrm{pH} \quad . \quad . \quad . \quad . \quad (9)$$

The reasons advanced by Israel *et al.* (*loc. cit.*) for the variation of the rate constants in their velocity equation (2) should be applicable to equation (8) for crotonic acid. Thus $\partial k_a/\partial \mathrm{pH} > 0$ and $\partial k_b/\partial \mathrm{pH} < 0$. Shilov and Kanyaev (*J. Phys. Chem. Russia*, 1934, **5**, 654) found that the rate constant in the equation derived by them, *viz.*, $v = k[\mathrm{HOCl}]^2[R{\cdot}CO_2H]$, decreased with increasing pH and, extending this finding to k_c, we see that $\partial k_c/\partial \mathrm{pH} < 0$. Thus since the terms on the right-hand side of equation (9) differ in sign, it would be possible for $\partial v/\partial \mathrm{pH}$ to change from positive to negative with changes in the total olefin concentration. The partial derivatives of the first three terms in equation (9) with respect to total olefin concentration are constants (or zero). The last term, however, is the controlling factor and an examination of Table 2 shows that the variation of $\partial[R{\cdot}CO_2H]/\partial \mathrm{pH}$ with total olefin concentration is not constant, but increases markedly with total olefin concentration. Now $\partial[R{\cdot}CO_2H]/\partial \mathrm{pH}$ is negative and hence for large concentrations of olefin, this term becomes larger in magnitude (still retaining its negative sign) with the result that the other constant positive terms are exceeded to such an extent that $\partial v/\partial \mathrm{pH}$ decreases through zero, eventually to become negative.

It is possible to predict where this reversal of sign will take place; it will be near the pK_a value for crotonic acid (4·69) since it is here that the change $\partial[R{\cdot}CO_2H]/\partial \mathrm{pH}$ is a maximum. This is in agreement with the experimental findings given in Table 2.

It has been shown that the general velocity equations at 25° and 35° are similar, and thus the explanation of the variation of the velocity with pH at 25° should be applicable to a change in pH at 35°. Examination of Table 3 supports this view.

The author acknowledges helpful criticisms by Dr. J. A. Allen and the award by the University of Tasmania of a Commonwealth Research Studentship.

UNIVERSITY OF TASMANIA, HOBART, TASMANIA.
[Present address : DIVISION OF APPLIED CHEMISTRY, N.R.C., OTTAWA, CANADA.]

[*Received, November 23rd*, 1953.]

The Kinetics of Chlorohydrin Formation. Part VI. The Reaction between Hypochlorous Acid and Tiglic Acid at Constant* pH.

By D. A. Craw.

[Reprint Order No. 4824.]

The kinetics of the reaction between hypochlorous acid and tiglic acid in the presence of sodium tiglate have been investigated in aqueous solution of constant pH 4·73 at 25·00° ± 0·01° and 35·00° ± 0·01°. The reaction conforms to the velocity equation

$$v = k_2^{I}[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-]) + k_2^{II}[HOCl]^2$$

where R = $CH_3{\cdot}CH{:}CMe{\cdot}$. The significance and the temperature dependence of the rate constants k_2^{I} and k_2^{II} are discussed. The values for the specific rate constants and the activation energies for the addition of hypochlorous acid to tiglic acid are given and compared with those for crotonic acid (Craw and Israel, *J.*, 1952, 550; Part V *).

The kinetics of the addition of hypochlorous acid to tiglic acid have not previously been investigated although the electrophilic addition of bromine and the nucleophilic addition of bromine catalysed by hydrogen bromide in acetic acid solution have been studied (Anantakrishnan and Venkataraman, *Proc. Indian Acad. Sci.*, 1940, **12**, *A*, 290; 1946, **23**, *A*, 312; Evans, Watson, and Robertson, *J.*, 1950, 1624). This work indicated that tiglic acid reacted 6—10 times faster than crotonic acid.

The products of the reaction between hypochlorous acid and tiglic acid have been studied by Melikov (*Annalen*, 1886, **234**, 224; 1890, **257**, 119) and by Bloomfield, Farmer, and Hose (*J.*, 1933, 800) who were interested in the relative amounts of the chloro-hydroxy-isomers formed. They observed that the addition to both the free acid and the sodium salt was rapid compared with that to crotonic acid and yielded water-soluble chlorohydrins, the β-chloro-α-hydroxy-isomer predominating.

In view of the satisfactory velocity equation developed for crotonic acid (*locc. cit.*), a similar kinetic investigation was applied to tiglic acid to study the effect of the α-methyl substituent.

Experimental

Materials.—Tiglic acid, from B.D.H., was recrystallised from water; it had m. p. 64·5°. A stock tiglic acid–sodium tiglate buffer solution in which the ratio $[R{\cdot}CO_2^-]_0/[R{\cdot}CO_2H]_0 = 0{\cdot}513$ where R = $CH_3{\cdot}CH{:}CMe{\cdot}$ was prepared. This ratio was the theoretical value for a resultant pH of 4·73 (Ostwald, *Z. physikal. Chem.*, 1888, **3**, 242) and was kept constant throughout in order to minimise the effects of pH on the rate of addition. The application of Pitzer's equation (*J. Amer. Chem. Soc.*, 1937, **59**, 2365) for variation of the dissociation constant of weak acids with temperature gave a pK_a value of 5·01 at 35° compared with 5·02 at 25°. This change was negligible and hence the same stock buffer solution was used at both these temperatures.

Hypochlorous acid was prepared by two different methods, one of which was described in the preceding paper. The other preparation was the non-aqueous method of Ourisson and Kastner (*Cong. Chim. ind., Compt. rend. XVIII Congr.*, Sept. 1938, p. 983) in which chlorine was passed into an agitated suspension of mercuric oxide in carbon tetrachloride at 0°. The reddish-brown solution of chlorine monoxide in carbon tetrachloride was shaken with yellow mercuric oxide, filtered, and stored at 4°. Fresh hypochlorous acid was prepared by extracting a small portion of this solution with water, but, as this aqueous extract usually smelt slightly of chlorine, it was always treated at least twice with freshly precipitated bismuth hydroxide and filtered.

Kinetic Measurements.—These were carried out by Israel, Martin, and Soper's method (*J.*, 1950, 1282). The greater reactivity of this olefin necessitated sampling at half-minute intervals.

Results

The pH was measured 5 min. after the reaction was started and in all cases was slightly lower than the theoretical initial value of 4·73. The pH deviation increased with increasing

* Part V, preceding paper.

hypochlorous acid concentration and may be explained by the rapid addition of hypochlorous acid to sodium tiglate, thereby altering the constitution of the buffer, and also by the presence of chloro-hydroxy-α-methylbutyric acids.

The symbol R below represents always $CH_3 \cdot CH{:}CMe$; concentrations are expressed in moles $l.^{-1}$ and velocities in moles $l.^{-1}$ $min.^{-1}$.

Eleven series each of approximately constant initial hypochlorous acid concentration were studied at 25·00° ± 0·01° and the results listed in Table 1.

TABLE 1.

Run no.	$[HOCl]_0 \times 10^3$	$([R\cdot CO_2H]_0 + [R\cdot CO_2^-]_0) \times 10^3$	$v_0 \times 10^5$ obs.	$v_0 \times 10^5$ calc.
A1	0·61	1·0	1·59	1·52
A2	0·61	2·0	2·82	2·75
A3	0·61	4·0	5·00	5·17
A4	0·60	6·0	7·55	7·61
A5	0·61	8·0	10·2	10·1
B1	0·91	1·0	2·51	2·46
B2	0·91	2·0	4·42	4·28
B3	0·90	4·0	8·03	7·93
B4	0·90	6·0	11·7	11·6
B5	0·90	8·0	15·7	15·3
C1	1·09	1·0	3·03	3·10
C2	1·09	2·0	5·13	5·31
C3	1·09	4·0	9·67	9·69
C4	1·09	6·0	13·9	14·1
C5	1·08	8·0	18·3	18·4
D1	1·31	1·0	3·88	3·94
D2	1·31	2·0	6·50	6·59
D3	1·31	4·0	11·8	11·8
D4	1·30	6·0	17·1	17·1
D5	1·30	8·0	22·3	22·4
E1	1·35	1·0	4·25	4·10
E2	1·34	2·0	6·57	6·77
E3	1·33	4·0	11·9	12·1
E4	1·33	6·0	17·1	17·4
E5	1·33	8·0	22·6	22·8
F1	1·57	1·0	4·88	5·02
F2	1·56	2·0	8·15	8·16
F3	1·56	4·0	14·5	14·4
F4	1·56	6·0	21·1	20·7
F5	1·56	8·0	28·0	27·0
G1	1·68	1·0	5·33	5·52
G2	1·68	2·0	8·45	8·89
G3	1·66	6·0	21·0	22·3
G4	1·66	8·0	28·5	29·0
H1	1·78	1·0	6·28	5·98
H2	1·77	2·0	9·45	9·54
H3	1·76	4·0	16·4	16·6
H4	1·76	6·0	23·2	23·7
H5	1·76	8·0	30·4	30·9
I1	1·89	1·0	6·18	6·49
I2	1·88	2·0	10·0	10·3
I3	1·88	4·0	17·3	17·8
I4	1·87	6·0	24·7	25·3
I5	1·87	8·0	32·5	32·9
J1	1·96	1·0	6·99	6·85
J2	1·96	2·0	11·2	10·8
J3	1·95	4·0	18·8	18·6
J4	1·95	6·0	28·0	26·5
J5	1·94	8·0	35·0	34·3
K1	2·01	1·0	7·04	7·08
K2	2·00	2·0	11·1	11·1
K3	1·99	4·0	19·2	19·1
K4	1·99	6·0	27·3	27·1
K5	1·99	8·0	35·5	35·1

The variation of the initial velocity, v_0, with the total olefin concentration for constant initial hypochlorous acid concentration was investigated as described in the preceding paper and can be represented by the equation,

$$v_0 = k([R\cdot CO_2H]_0 + [R\cdot CO_2^-]_0) + v_{res} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Values of k and v_{res} were evaluated for each series by the method of least squares, and their variation with the concentration of hypochlorous acid can be expressed by the equations

$$k = 20{\cdot}24[HOCl]_0 - 0{\cdot}007 \times 10^{-2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and

$$v_{res} = 7{\cdot}49[HOCl]_0^2 - 0{\cdot}04 \times 10^{-5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The constant terms in these equations may be rejected without serious error, whence

$$k = k_2^{I}[HOCl]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and

$$v_{res} = k_2^{II}[HOCl]_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Thus the complete velocity equation becomes

$$v_0 = k_2^{I}[HOCl]_0([R\cdot CO_2H]_0 + [R\cdot CO_2^-]_0) + k_2^{II}[HOCl]_0^2 \quad . \quad . \quad . \quad (6)$$

or by substitution of the values of the rate constants and expression of the equation generally,

$$v = 20{\cdot}2[HOCl]([R\cdot CO_2H] + [R\cdot CO_2^-]) + 7{\cdot}5[HOCl]^2 \quad . \quad . \quad . \quad (7)$$

The observed initial velocities compare reasonably with those calculated by equation (6) (see Table 1).

The satisfactory nature of this equation prompted an investigation at 35·00° ± 0·01°, and the nine series A′—I′ given in Table 2 resulted.

TABLE 2. Initial pH = 4·73. Temperature = 35·00° ± 0·01°.

Run no.	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	$v_0 \times 10^5$ obs.	calc.	Run no.	$[HOCl]_0$ $\times 10^3$	$([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0)$ $\times 10^3$	$v_0 \times 10^5$ obs.	calc.
A′1	1·02	1·0	4·68	4·70	F′1	2·00	1·0	10·9	11·5
A′2	1·02	2·0	8·60	8·28	F′2	2·00	2·0	18·4	18·4
A′3	1·01	4·0	15·8	15·2	F′3	1·98	4·0	31·5	31·9
A′4	1·01	6·0	22·6	22·2	F′4	1·97	6·0	44·6	45·6
A′5	1·01	8·0	30·5	29·2	F′5	1·97	8·0	59·0	59·3
B′1	1·27	1·0	6·61	6·21	G′1	2·21	1·0	13·0	13·2
B′2	1·26	2·0	10·7	10·5	G′2	2·21	2·0	21·1	20·9
B′3	1·25	4·0	19·6	19·1	G′3	2·17	4·0	33·9	35·5
B′4	1·23	6·0	27·0	27·3	G′4	2·18	6·0	51·8	50·9
B′5	1·24	8·0	37·7	36·3	G′5	2·15	8·0	65·9	65·3
C′1	1·26	1·0	6·68	6·20	H′1	2·50	1·0	15·7	15·8
C′2	1·25	2·0	10·6	10·5	H′2	2·50	2·0	24·7	24·4
C′3	1·25	4·0	20·7	19·2	H′3	2·46	4·0	39·5	41·1
C′4	1·24	6·0	28·8	27·7	H′4	2·45	6·0	56·8	58·0
C′5	1·24	8·0	37·8	36·2	H′5	2·45	8·0	75·7	75·0
D′1	1·51	1·0	7·81	7·80	I′1	2·81	1·0	18·6	18·6
D′2	1·50	2·0	12·7	12·9	I′2	2·79	2·0	26·1	28·1
D′3	1·49	4·0	23·5	23·3	I′3	2·77	4·0	45·4	47·2
D′4	1·48	6·0	33·6	33·3	I′4	2·73	6·0	62·1	65·5
D′5	1·48	8·0	45·0	43·7	I′5	2·73	8·0	82·3	84·4
E′1	1·87	1·0	10·8	10·4					
E′2	1·85	2·0	16·6	16·7					
E′3	1·84	4·0	29·6	29·4					
E′4	1·83	6·0	42·5	42·1					
E′5	1·82	8·0	55·8	54·5					

As previously, the variation of the initial velocity with the initial total olefin concentration for constant hypochlorous acid concentration was examined graphically and the line of best fit determined by the method of least squares. This variation may be represented for each of the series A′—I′ by

$$v_0 = k'([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0) + v'_{res} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

The variation of k' with hypochlorous acid concentration was nearly linear but a slight decrease in the value of $k'/[HOCl]_0$ is noticed in the values tabulated below:

Series	$k'/[HOCl]_0$	Series	$k'/[HOCl]_0$	Series	$k'/[HOCl]_0$	Series	$k'/[HOCl]_0$
A′	35·98	D′	35·56	G′	34·71	I′	32·94
B′	35·00	E′	34·98	H′	34·20	Mean:	34·86
C′	36·12	F′	34·22				

For this reason, the method of least squares was not used to determine the equation of this graph, but the arithmetic mean of the $k'/[HOCl]_0$ values enabled the variation of k' with hypochlorous acid concentration to be represented by the equation

$$k' = 34{\cdot}86[HOCl]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

i.e.,

$$k' = k_2^{I}[HOCl]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The residual velocity, v'_{res}, varied with the hypochlorous acid concentration according to the equation

$$v'_{res} = 11{\cdot}20[HOCl]_0^2 + 0{\cdot}053 \times 10^{-5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

and, rejecting this constant term as small compared with the observed velocities, we obtain the relation

$$v'_{res} = k_2^{II}[HOCl]_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Thus the complete velocity equation is

$$v = k_2^{I}[HOCl]_0([R{\cdot}CO_2H]_0 + [R{\cdot}CO_2^-]_0) + k_2^{II}[HOCl]_0^2 \quad . \quad . \quad . \quad (13)$$

Substituting of the values for the rate constants and expressing the equation generally gives

$$v = 34{\cdot}9[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-]) + 11{\cdot}2[HOCl]^2 \quad . \quad . \quad . \quad (14)$$

A comparison of the observed velocities with those calculated by equation (13) shows that this equation represents the initial course of the reaction with reasonable accuracy.

A comparison of the times for a certain percentage decrease in the hypochlorous acid concentration obtained from the observed data and from the integration of equations (7) and (14) showed satisfactory agreement. The generalisation of the initial velocity equations (6) and (13) to equations (7) and (14) was, therefore, justified.

Discussion

In the general velocity equation, the term $k_2^{I}[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-])$ represents, as in the case of crotonic acid, contributions from a number of simultaneous reactions concerned with the direct attack of hypochlorous acid on either undissociated tiglic acid or tiglate ion and with the possible rate-determining formation of α-methylcrotonyl hypochlorite.

The only other term found in this equation, $k_2^{II}[HOCl]^2$, probably represents the rate of formation of chlorine monoxide from hypochlorous acid.

No term involving the product $[HOCl]^2[R{\cdot}CO_2H]$ was found for the tiglic acid reaction. In the case of crotonic acid (*locc. cit.*) this term had been explained as the acid-catalysed formation of chlorine monoxide from hypochlorous acid. It is strange that such a term does not occur for tiglic acid whose strength is approximately the same as that of crotonic acid. Other reactions could take place to account for this term, but they must be capable of explaining its occurrence with allyl alcohol (Israel, *J.*, 1950, 1286) and crotonic acid and its non-inclusion in the velocity equations for the more reactive tiglic and ββ-dimethylacrylic acid. That is, the rate-determining step of any set of composite reactions evolved to explain this finding must be influenced by the reactivity of the olefin.

Consider the following reactions:

$$2HOCl \rightleftharpoons Cl_2O + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

$$R{\cdot}CO_2H + Cl_2O \longrightarrow R{\cdot}CO{\cdot}OCl + HOCl \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

$$R{\cdot}CO{\cdot}OCl + R{\cdot}CO_2H \longrightarrow (R'{\cdot}CO_2H)^+ + R{\cdot}CO_2^- \quad . \quad . \quad . \quad (iii)$$

where $R' = CH_3{\cdot}CHCl{\cdot}CMe{\cdot}$ or $CH_3{\cdot}CH{\cdot}CMeCl{\cdot}$. These equations provide a probable solution to the problem provided the formation of acyl hypochlorites by step (ii) is slower in the case of acetic and crotonic acids than the formation of chlorine monoxide by step (i), and faster than this forward reaction in the case of tiglic and ββ-dimethylacrylic acids. In this latter case, the chlorine monoxide is used up as fast as it is formed and step (i) becomes rate-determining. However, our knowledge of the relative rates of the reactions above is limited by the small amount of information available about these acyl hypochlorites.

If we assume absence of change in the non-exponential coefficient of the Arrhenius equation in the temperature interval from 25° to 35°, the activation energies for the separate processes involving k_2^{I} and k_2^{II} calculated from the ratios of the rate constants at the two temperatures are 9·89 and 7·33 kcal. mole^{-1} respectively. The corresponding values for crotonic acid were 8·38 and 9·87 respectively. The probability factor, P, was calculated for both tiglic and crotonic acid to see whether the increased value for the rate constant k_2^{I} was due to an increase in the activation energy, to a change in the probability factor, or to both. The value of P for tiglic acid was about 68 times that for crotonic acid and thus the higher value of k_2^{I} for tiglic acid can be attributed to changes in both the activation energy and P. This is not surprising as the presence of a methyl group near the point of attack would cause disturbances of both an electrical and a geometrical character. The presence of the α-methyl substituent in tiglic acid increased the rate of attack by hypochlorous acid almost five-fold.

Where the variation in P is of prime importance, a change in the mechanism of a reaction is suspected. The variable nature of k_2^{II}, which should be independent of the olefin, with the olefin persisted, and this may be due to a change in mechanism where the absence of the term $k_3^{II}[HOCl]^2[R{\cdot}CO_2H]$ for the tiglic acid equation results in an increased contribution from the term $k_2^{II}[HOCl]^2$ with a subsequent effect on k_2^{II}.

The author acknowledges the helpful suggestions by Mr. G. C. Israel and Mr. K. D. Reeve and the award by the University of Tasmania of a Commonwealth Research Studentship.

UNIVERSITY OF TASMANIA, HOBART, TASMANIA.
[Present address: DIVISION OF APPLIED CHEMISTRY, N.R.C., OTTAWA, CANADA.]

[*Received, November 23rd*, 1954.]

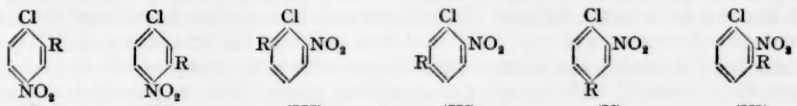
The Reaction Velocity of Some Substituted o- *and* p-*Chloronitrobenzenes with Piperidine.*

By JORGE A. BRIEUX and VENANCIO DEULOFEU.

[Reprint Order No. 5064.]

The velocity constants for the reactions of some monosubstituted (R = Me, OMe and OEt) *o*- and *p*-chloronitrobenzenes with piperidine in benzene at 100° have been determined. Possible reasons for the order of reactivity are given.

PREVIOUSLY (*Chem. and Ind.*, 1951, 971; *Anal. Asoc. Quím. Argentina*, 1951, **39**, 195) we recorded the velocity of the reaction of *o*- and *p*-chloro-, -bromo-, and -iodo-nitrobenzene with piperidine in benzene. We have now studied the changes in the reaction velocity



at 100° when a methyl, methoxy-, or ethoxy-group is introduced into the benzene ring of *o*- and *p*-chloronitrobenzene.

The results for compounds of type (I—VI) are given in Table 1.

TABLE 1. *Reaction velocities of substituted* p- *and* o-*chloronitrobenzenes with piperidine at* 100° ± 0·1°. *Values of* 10^7k (l. mole^{-1} sec.$^{-1}$).

Halogenonitrobenzene		Me	OMe	OEt
p-Chloronitrobenzene	16·8	—	—	—
(I) 2-R-1-Chloro-4-nitrobenzene	—	0	7·0	4·16
(II) 2-R-4-Chloro-1-nitrobenzene	—	3·6	14·1	4·45
o-Chloronitrobenzene	779	—	—	—
(III) 1-R-2-Chloro-3-nitrobenzene	—	5·55	152	123
(IV) 4-R-2-Chloro-1-nitrobenzene	—	772	2630	1820
(V) 4-R-1-Chloro-2-nitrobenzene	—	152	35·9	30·2
(VI) 1-R-3-Chloro-2-nitrobenzene	—	12·1	23·3	9·73

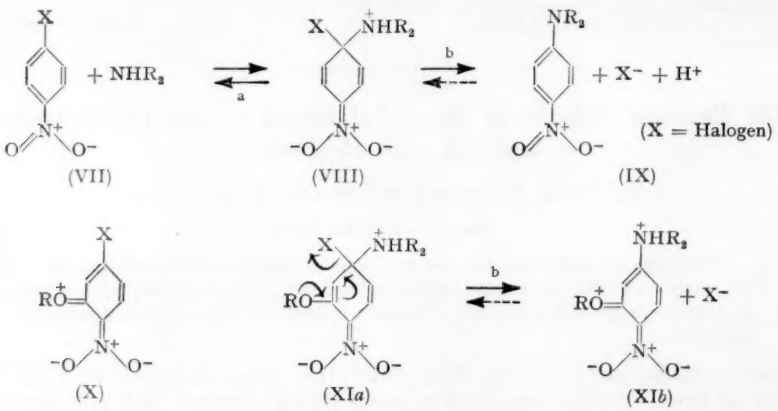
DISCUSSION

The mechanism of nucleophilic substitution of halogen in nitroaryl halides has been considered recently (Bevan, *J.*, 1951, 2340; Chapman and Parker, *J.*, 1951, 3301; Beckwith, Miller, and Leahy, *J.*, 1952, 3555; Berliner and Monack, *J. Amer. Chem. Soc.*, 1952, **74**, 1574). Substitution in *o*- and *p*-nitroarylhalides (VII) probably occurs through an intermediate complex of general type (VIII) (Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 293).

The overall effect of a substituent in various positions in (VII) on the velocity of halogen displacement appears to be mainly the resultant of the following factors.

Polar factors. (i) An electron-releasing substituent *ortho* to halogen will, by decreasing the positive character of the carbon atom to which the halogen is attached, reduce its susceptibility to nucleophilic attack.

(ii) A substituent with a $+M$ effect *ortho* to the activating nitro-group may increase the energy of formation of (VIII) because of the necessary loss of resonance energy, in (VII) arising from the incidence of structures of type (X), which are impossible in (VIII). In this respect the first-order conjugation of an alkoxy-group will be greater than the first-order hyperconjugation of an alkyl group.



(iii) In the intermediate complex (XI*a*), however, the presence of such $+M$ groups, which are also *meta* to the halogen, should increase the negative character of the halogen by incidence of structures of type (XI*b*) and thus facilitate the breakdown of (VIII) in the direction b by lowering the energy barrier over which the complex has to pass to give halogen displacement. Alkoxy-groups so placed might have a powerful accelerating action; *p*-quinonoid structures, being regarded as more stable, are more effective than *o*-quinonoid.

Steric factors. (iv) Primary steric effects and (v) secondary steric effects both as defined by Ingold ("Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, pp. 402, 803). Although a *p*-nitroaryl halide has been used in illustration the same features will apply to the *o*-nitro-compounds. Estimation of the relative magnitudes and importance of the various factors is difficult and only a qualitative assessment of the resultant effect for any particular substituent is possible. It will be noticed that, with three exceptions, alkyl and alkoxy-substituents diminish the reaction velocity in both *o*- and *p*-chloronitrobenzene.

In compounds of type (IV) and (V) the effect of substituents is free from steric factors and, of these, only compounds of type (V) have been studied in detail (cf. Berliner and Monack, *loc. cit.*; Miller, *J.*, 1952, 3550). In compounds of type (IV) factors (ii) and (iii) are operative while in those of type (V) the effect of the substituent should be mainly attributed to (i). The ratio $k_{(V;\ R)}/k_{(o\text{-}NO_2)}$ gives the relative effect of the *p*-substituent at a certain temperature under established experimental conditions. Our values for this ratio are: Me, 0·196; OMe, 0·046; OEt, 0·039. The fact that methyl substitution in 2-chloro-4-methyl-1-nitrobenzene has no retarding or accelerating effect but similarly placed alkoxy-groups in 2-chloro-4-methoxy- and -4-ethoxy-1-nitrobenzene produce a very marked acceleration suggests that such acceleration is due mainly to a very powerful effect (iii) by these substituents, the smaller (hyperconjugative) effect of the similarly placed methyl group being sufficient only to counteract its other retarding influences. The results suggest that for the alkoxy-groups the effect (ii) has no great influence on the rate of reaction in spite of the opposite mesomeric character of the alkoxy- and the nitro-group situated *para* each other (cf. Robinson, *J.*, 1947, 1288; Dewar, *J.*, 1949, 468).

The overall effect of R in compounds of type (I, II, III, and VI) is not free from steric influences and in some cases they are important.

The complete lack of measurable activity in 1-chloro-2-methyl-4-nitrobenzene is in broad agreement with Spitzer and Wheland's results (*J. Amer. Chem. Soc.*, 1940, **62**, 2995) for methyl-substituted *p*-bromonitrobenzenes. A strong deactivating effect of the methyl group when *ortho* to two nitro-groups and *meta* to the halogen atom has been described by Lindemann and Pabst (*Annalen*, 1928, **462**, 24) who found that 3-halogeno-2 : 6-dinitrotoluenes do not react with aniline under the conditions of their experiments.

Miller and Williams (*J.*, 1953, 1476) compared the reaction rate of some substituted chloronitro- and chlorodinitro-benzenes with sodium methoxide in methanol and concluded that in the *ortho*-effect of methyl groups geometrical hindrance is unimportant.

The ratio k_V/k_{III} which is similar but not equivalent to the " steric index " defined by them measures the *ortho*-effect of R in the monosubstituted chloronitrobenzenes (Me, 27·4; OMe, 0·236; OEt, 0·246). The high value of this ratio for the methyl group suggests that the low reactivity of 2-chloro-3-nitrotoluene must be mainly due to primary steric retardation (iv) since, according to the figures quoted by Ingold (*op. cit.*, p. 259) for the rates of attack on the individual positions of toluene and *tert.*-butylbenzene in nitration, the transfer of charge by the methyl group to the *ortho*- and *para*-positions can be interpreted as fairly constant. The difference between the ratios $k_{(o\text{-}NO_2)}/k_{(V;\ Me)}$ and $k_{(V;\ Me)}/k_{(III;\ Me)}$ is large enough to support our view. The same considerations apply to 2-chloro-5-nitrotoluene where factors (i) and (iv) also operate.

The reactivity of the 1-alkoxy-2-chloro-3-nitrobenzenes and of 2-alkoxy-1-chloro-4-nitrobenzenes cannot be interpreted unambiguously. The low value of $k_{(V;\ OR)}/k_{(o\text{-}NO_2)}$ suggests an accelerative contribution of the alkoxy-group *ortho* to the chlorine but as quinonoid structures are probably more important for transfering charges to the *para*- than to the *ortho*-position (de la Mare, *J.*, 1949, 2871) the relative importance of factors (i) and (iv) cannot be assessed. The interpretation of the data for compounds of types (II) and (VI) is complicated but it can be observed that factor (iii) if operative does not compensate for retarding factors.

The sequence of our results with the different chloronitrotoluenes derived from *o*-chloronitrobenzene agrees with that obtained by Campbell, Anderson, and Gilmore (*J.*, 1940, 446) for some bromonitrotoluenes with piperidine as reagent and solvent. From their figures of the percentage removal of bromine at 45° during 1 hr., the ratios of reactivities, *o*-bromonitrobenzene/4-bromo-3-nitrotoluene and 4-bromo-3-nitrotoluene/2-bromo-3-nitrotoluene, 4 and 13 respectively, show that the overall effect of the methyl group *ortho* to the halogen is mainly steric. As their experiments and ours differ widely in experimental conditions, temperature, solvent, and halogen substituent, the structure of the compounds and the reagent being common, this conclusion seems well established.

The different conclusion drawn by Miller and Williams can be related to the reagent employed but in our view the simplification made by these authors of comparing compounds related to different reference compounds is not justified, as in this way the basic requirement of keeping the activating system unchanged is not fulfilled.

Experimental

Materials.—Commercial *o*- and *p*-chloronitrobenzene were purified by recrystallisation and had m. p. 32·5° and 84° respectively. The substituted chloronitrobenzenes were prepared by methods described in the literature. 4-Chloro-2-methoxy- and -2-ethoxynitrobenzene were made from *m*-chloronitrobenzene in two stages, the first according to Laubenheimer (*Ber.*, 1876, **9**, 760) and the second to Blanksma (*Rec. Trav. chim.*, 1902, **21**, 332). The intermediate 4-chloro-1 : 2-dinitrobenzene had m. p. 40° (methanol) (lit., 37°). For all the other chloronitro-compounds the last stage was a Sandmeyer reaction with the corresponding nitro-amine by Hodgson and Walker's method (*J.*, 1933, 1620). The chloro-compounds were distilled *in vacuo* or crystallised to constant m. p. shortly before use and had the following m. p.s or b. p.s: 2-chloro-5-nitrotoluene, m. p. 43—43·5°; 5-chloro-2-nitrotoluene, m. p. 25°; 2-chloro-3-nitrotoluene, b. p. 147°/25 mm.; 3-chloro-4-nitrotoluene, b. p. 145°/43 mm.; 4-chloro-3-nitrotoluene, m. p. 7°, b. p. 141°/25 mm.; 3-chloro-2-nitrotoluene, b. p. 127°/24 mm.; 2-chloro-

5-nitroanisole, m. p. 83°; 5-chloro-2-nitroanisole, m. p. 73°; 2-chloro-3-nitroanisole, m. p. 94—95°; 3-chloro-4-nitroanisole, m. p. 32°; 4-chloro-3-nitroanisole, m. p. 44—45°; 3-chloro-2-nitroanisole, m. p. 55°; 2-chloro-5-nitrophenetole, m. p. 64·5—65·5°; 5-chloro-2-nitrophenetole, m. p. 63°; 2-chloro-3-nitrophenetole, m. p. 50—51°; 3-chloro-4-nitrophenetole, m. p. 40—41°; 4-chloro-3-nitrophenetole, m. p. 49—50°; 3-chloro-2-nitrophenetole, m. p. 52°. Piperidine was dried over potassium hydroxide and distilled through an efficient column. The fraction of b. p. 106—107·5°/760 mm. was collected. Benzene was purified according to Haller and Michael (*Bull. Soc. chim.*, **1896**, **15**, 1065).

Method.—For each compound, four or five glass tubes, each containing 20 c.c. of a benzene solution about 1M with respect to piperidine and 0·1M to the chloro-compound were sealed and placed simultaneously in the thermostat controlled to 100° ± 0·1° and when the temperature inside, taken as that shown by a thermometer in a sealed tube containing benzene, reached 100° one of the tubes was removed and cooled in ice-water. The contents were extracted with 20 c.c. of 10% nitric acid, and the halide ion was determined potentiometrically. The other tubes were removed at convenient times and treated in the same way.

The rate constants were calculated by the equation, $k = \{2{\cdot}303/[t(b - 2a)]\} \log_{10} \{a(b - 2x)/[b(a - x)]\}$ for the overall reaction

$$NO_2{\cdot}C_6H_3R{\cdot}Cl + 2C_5H_{10}NH \longrightarrow NO_2{\cdot}C_6H_3R{\cdot}NC_5H_{10} + C_5H_{10}NH{\cdot}ClH$$

where a and b are the initial concentrations of halogenonitrobenzene and piperidine, and x is the halide concentration at time t.

The following are two typical runs for 2-chloro-3-nitrophenetole,

a (mole/l.)	b (mole/l.)	x (mole/l.)	t (sec.)	10^7k (l. mole^{-1} sec.$^{-1}$)	a (mole/l.)	b (mole/l.)	x (mole/l.)	t (sec.)	10^7k (l. mole^{-1} sec.$^{-1}$)
0·0973	0·9658	0·0003	—	—	0·0973	1·0087	0·0002	—	—
		0·0139	12,600	125·9			0·0091	7,680	125·2
		0·0173	16,200	125·0			0·0157	14,450	121·2
		0·0580	84,000	119·1			0·0576	77,400	122·4
			Mean	123·3				Mean	122·9

The mean deviation of the mean for the reaction rates lies in the range 2—3%. Figures in Table 1 are the mean values of at least two independent runs.

The authors are indebted to Dr. J. W. Baker for helpful suggestions on the presentation of this paper, to "Sociedad Científica Argentina" and "Cámara Gremial de la Industria Química" for scholarships awarded to one of them (J. A. B.).

CÁTEDRA DE QUÍMICA ORGÁNICA, FACULTAD DE CIENCIAS EXACTAS Y NATURALES,
BUENOS AIRES, ARGENTINA. [*Received, January* 26*th*, 1954.]

The Hemicelluloses of Scots Pine (Pinus sylvestris) *and Black Spruce* (Picea nigra) *Woods.**

By A. R. N. GORROD and J. K. N. JONES.

[Reprint Order No. 5069.]

Acid hydrolysis of extractive-free wood of Scots Pine and Black Spruce has yielded 2-*O*-(4-*O*-methyl-D-glucosidurono)-D-xylose, 4-*O*-methyl-D-glucuronic acid, and D-galacturonic acid. The neutral sugars were D-xylose, L-arabinose, D-mannose, D-galactose, L-rhamnose, and L-fucose. Small amounts of 3-*O*-methyl-L-rhamnose and glucurone were isolated from the hydrolysate from Black Spruce wood.

EXTRACTIVE-FREE woods of the two species, Scots Pine (*Pinus sylvestris*) and Black Spruce (*Picea nigra*), have been partially hydrolysed with dilute sulphuric acid, and the products investigated. It was of interest to compare the results obtained from the hydrolysis of these two soft woods with those obtained from the hydrolysis of Aspen wood (Jones and

* A brief account of certain aspects of this work was presented at the XIIIth International Congress of Pure and Applied Chemistry, Stockholm, July, 1953.

Wise, *J.*, 1952, 2750). It seems that the apparent difference between these three woods is that 3-*O*-methyl-L-rhamnose and D-glucurone are found in the monosaccharide fraction from Black Spruce wood, albeit in minute quantities, and that L-fucose has not been isolated from aspen wood. L-Fucose occurs in small amounts in many gums and mucilages, notably gum tragacanth (cf. James and Smith, *J.*, 1945, 739). The neutral and acidic fractions were separated and identified as described by Jones and Wise (*loc. cit.*). The 3-*O*-methyl-L-rhamnose was isolated as the crystalline sugar and identified by its rate of movement on the chromatogram (Dunstan and Hirst, *J.*, 1953, 2332) and by the identity of its *X*-ray diffraction pattern with that of an authentic specimen. Black Spruce wood contains quantities of materials which are soluble in benzene and ethanol. Samples of alcohol- and benzene-soluble material were isolated and hydrolysed; 3-*O*-methyl-L-rhamnose was not detected in the hydrolysate. It is inferred that this sugar is not a component of the extractives of wood but that it is probably a component of a polysaccharide. This is the first time this derivative of L-rhamnose has been encountered as a component of a natural product. It is noteworthy that the methoxyl group is on $C_{(3)}$ and that every methylated sugar so far encountered in Nature, with the exception of 4-*O*-methyl-D-glucuronic acid, has its methoxyl on $C_{(3)}$ (Hough and Jones, *Nature*, 1951, **167**, 180). It is possible that D-glucuronic acid may arise from D-glucose by an inversion of hydroxyl groups in which $C_{(1)}$ of the glucose becomes $C_{(6)}$ of the glucuronic acid and that 4-*O*-methyl-D-glucuronic acid arises from 3-*O*-methyl-D-glucose by a similar inversion (cf. the origin of vitamin C; Isherwood *et al.*, *Biochem. J.*, 1954, **561**). This possibility is being investigated.

Other sugars and sugar acids remain to be identified in the mixture of sugars prepared from these woods and it may be that such identification will throw some light on the reason for the different physical and chemical properties of these woods.

Experimental

Paper chromatography was carried out by the descending method (Partridge, *Biochem. J.*, 1948, **42**, 238) on Whatman No. 1 filter paper, the following solvent systems being used: (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4), (*b*) *n*-butanol–pyridine–water (10 : 3 : 3), (*c*) *n*-butanol–ethanol–water (40 : 11 : 19); all v/v. The positions of the sugars on the chromatograms were determined by the use of ammoniacal silver nitrate spray (Partridge, *loc. cit.*) or *p*-anisidine hydrochloride spray (Hough, Jones, and Wadman, *J.*, 1950, 1702). The rates of movement of the sugars are approximate only and are quoted relative to that of a sugar of about the same mobility. Thus R_G, R_{RH}, R_X, or R_{gal} is the rate of movement of the sugar relative to 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, rhamnose, xylose, or galactose, respectively. Optical rotations were determined at 18° ± 2° in water and are equilibrium values unless otherwise stated. Solvents were removed under reduced pressure.

Examination of the Products of Hydrolysis of Pine Wood (Pinus sylvestris).—Sawdust (500 g.; extractive free; cf. Jones and Wise, *J.*, 1952, 2759) was washed with hot water (6 l.) during 2 hr., the washings were then colourless and gave only a faint Molisch test. The aqueous extract, which contained water-soluble polysaccharides, was examined separately (further details will be published later). The sawdust was pressed to remove as much water as possible and suspended in 2N-sulphuric acid (2 l.), and the slurry heated on the steam-bath for 10 hr; the bulk of the material was thus maintained at a temperature of about 60° during this time. The slurry was filtered and the residue washed with more hot water (2·5 l.). The combined filtrate and washings were brought to pH 3 (barium hydroxide), and the solution was filtered. The filtrate was passed through Amberlite resin 1R120, and the acidic effluent evaporated. The concentrate (500 c.c.) was passed through Amberlite resin 1R4B to remove acidic material, and the effluent, which contained the neutral sugars, was evaporated to a syrup (*A*; 10 g.). The acids were displaced from the Amberlite resin 1R4B with N-sulphuric acid, and the effluent solution neutralised (barium hydroxide) and filtered, and the filtrate passed through Amberlite resin 1R120. Concentration of this acidic effluent furnished a syrupy mixture of uronic acids (*B*; 2 g.).

Examination of syrup A. The syrup (10 g.) was fractionated on charcoal (Darco G60)–Celite (1 : 1; w/w) by elution first with water and then with aqueous ethanol (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677). The major fraction (6·5 g.), which was eluted with water, consisted of monosaccharides. Later fractions contained oligosaccharides of which xylobiose (30 mg.) was isolated after further fractionation on sheets of paper (solvent *c*). This substance had m. p. and mixed m. p. 183°, $[\alpha]_D$ −20°, and yielded xylose only on hydrolysis. A portion

(3·8 g.) of fraction *A* was refractionated on hydrocellulose (30 × 3·5 cm.), *n*-butanol half saturated with water being used as the mobile phase. Concentration of the appropriate portions of the effluent gave the following crystalline sugars: L-rhamnose, m. p. 95°, $[\alpha]_D$ +8°; D-xylose, m. p. 144°, $[\alpha]_D$ +18°; L-arabinose, m. p. 158°, $[\alpha]_D$ +100°; and D-galactose, m. p. 167°, $[\alpha]_D$ +80°. In addition, D-mannose was isolated and characterised as its phenylhydrazone, m. p. 189°, and L-fucose, $[\alpha]_D$ −70°, was characterised as its toluene-*p*-sulphonhydrazone, m. p. 172° (Easterby, Hough, and Jones, *J.*, 1951, 3416) (Found: C, 46·7; H, 6·0. $C_{13}H_{20}O_6N_2S$ requires C, 47·0; H, 6·0%). This substance was indistinguishable from an authentic specimen on *X*-ray crystallographic examination.

Examination of uronic acid fraction B. The uronic acids (2 g.) were placed on charcoal (Darco G60)–Celite (1 : 1; w/w) and eluted successively with water, 5% and then 10% ethanol, and finally with 20% acetic acid, and thus yielded fractions B_1 (0·13 g.), B_2 (0·79 g.), B_3 (0·50 g.), and B_4 (0·47 g.). Paper-chromatographic examination of these fractions (solvent *a*) indicated that B_1 contained 4-*O*-methylglucuronic acid and galacturonic acid, that fractions B_2 and B_3 consisted of these two acids, a uronic acid with R_X 0·73, and slower moving acids, and that fraction B_4 contained acidic oligosaccharides.

Fraction B_1 was freed from ash (Amberlite resin 1R120) and fractionated by chromatography on a sheet of filter paper. Elution of the appropriate sections of the paper gave D-galacturonic acid, m. p. 157°, $[\alpha]_D$ +110° ⟶ +40° (equilibrium value) [characterised after oxidation with bromine water as mucic acid, m. p. 215°, and as its 2 : 5-dichlorophenylhydrazone, m. p. and mixed m. p. 179° (Mandl and Neuberg, *Arch. Biochem. Biophysics*, 1952, **35**, 326)]. Fractions B_2 and B_3 were combined and fractionated on cellulose, *n*-butanol–formic acid (50 : 1, v/v) being used as eluant. The fastest-moving component (80 mg.) was 4-*O*-methyl-D-glucuronic acid, $[\alpha]_D$ +45°, R_{GH} 0·98, R_X 1·37 (solvent *a*), and was characterised as the amide of methyl 4-*O*-methyl-α-D-glucosiduronate, m. p. and mixed m. p. 230—235°. The next component to be eluted was 2-*O*-(4-*O*-methyl-α-D-glucosidurono)-D-xylose (*C*; 1·1 g.). Thereafter galacturonic acid and oligosaccharides were eluted (cf. Jones and Wise, *loc. cit.*).

Identification of the aldobiuronic acid, C (cf. Jones and Wise, *loc. cit.*). A portion (10 mg.) of this acid (*C*) was boiled with N-sulphuric acid (2 ml.) for 18 hr. (much decomposition occurred). The solution was neutralised (barium hydroxide) and filtered, and the filtrate examined on the paper chromatogram (solvent *a*). Xylose, 4-*O*-methyl-D-glucuronic acid, and the original disaccharide were identified.

The acid (*C*; 1·0 g.) was neutralised (barium hydroxide) and the solution evaporated to dryness. The barium salt showed $[\alpha]_D$ +80° [Found: Ba (as sulphated ash), 17·9; OMe, 6·7. Calc. for $(C_{12}H_{19}O_{11})Ba$: Ba (as sulphated ash), 16·8; OMe, 7·6%]. The barium salt (1·1 g.) was methylated with methyl sulphate and sodium hydroxide, and the methylated acid isolated as described by Jones and Wise (*loc. cit.*). This acid was further methylated with Purdie's reagent, and the product (500 mg.), $[\alpha]_D$ +105° ($CHCl_3$) (Found: OMe, 45·7. Calc. for $C_{18}H_{32}O_{11}$: OMe, 51·3%), was reduced with lithium aluminium hydride. The methylated disaccharide, which was isolated in the usual manner, was further methylated (sodium hydroxide and methyl sulphate) giving the fully methylated glucosidylxylose derivative (300 mg.), n_D^{18} 1·4644 (Found: OMe, 50·4. Calc. for $C_{18}H_{34}O_{10}$: OMe, 52·9%). The methylated disaccharide was boiled with N-sulphuric acid until the optical rotation of the solution had become constant {$[\alpha]_D$ +44° (*c*, 3·0) (18 hr.)}. The cooled solution was neutralised and extracted exhaustively with chloroform. Concentration of the extract yielded a syrup which contained two sugars, indistinguishable on paper chromatograms, in solvent *a*, *b*, or *c*, from 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and 3 : 4-di-*O*-methyl-D-xylose. These sugars were separated on sheet-paper chromatograms (solvent *c*) and identified as: (*a*) 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose (155 mg.), m. p. 90°, $[\alpha]_D$ +85° ($CHCl_3$) {the derived *N*-phenylglucosylamine 2 : 3 : 4 : 6-tetra-*O*-methyl ether had m. p. and mixed m. p. 137°, $[\alpha]_D$ +250° (Me_2CO)}, and (*b*) 3 : 4-di-*O*-methyl-D-xylose (61 mg.), $[\alpha]_D$ +30° ($CHCl_3$) (Found: OMe, 32·2. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). The latter was converted by oxidation with bromine water into 3 : 4-di-*O*-methyl-D-xylonolactone, m. p. and mixed m. p. 64° (from water).

Examination of the Products of Hydrolysis of Spruce Wood (Picea nigra).—Sawdust (700 g.; extractive free; cf. Jones and Wise, *loc. cit.*) was hydrolysed with 2N-sulphuric acid (3 l.) for 6 days on the steam-bath. The resultant solution was separated into a neutral fraction (*C*; 50 g.) and an acidic fraction (*D*; 12 g.) by the procedure described above (cf. Pine Wood hydrolysis).

The neutral sugars (*C*; 50 g.) were fractionated on cellulose, *n*-butanol half saturated with water being used as the mobile phase, and yielded the following crystalline sugars: L-rhamnose (trace), $[\alpha]_D$ 5°, m. p. 96°, m. p. 100° on admixture with an authentic specimen; D-xylose, $[\alpha]_D$

+18°, m. p. 144°; L-arabinose, $[\alpha]_D$ +102°, m. p. 158°; and D-galactose, $[\alpha]_D$ +80°, m. p. 167°. L-Fucose, identified as the toluene-*p*-sulphonhydrazone, m. p. 168°, the *X*-ray diffraction picture of which was identical with that of an authentic specimen, D-glucurone, m. p. and mixed m. p. 173—175°, and xylobiose (25 mg.), m. p. and mixed m. p. 183°, were detected after further fractionation of mixtures of sugars on sheet-paper chromatograms and were present in trace amounts. A quantity (30 mg.) of a methylated sugar, $[\alpha]_D$ +35° (Found: OMe, 13·4%), was also isolated. This material moved faster than rhamnose on the paper chromatogram (R_{RH} 1·38, 1·42, and 1·51 in solvents *a*, *b*, and *c*) and was indistinguishable from 3-*O*-methyl-L-rhamnose on the chromatogram. On nucleation with a specimen of this sugar the syrup crystallised; the solid had m. p. and mixed m. p. 113° (Found: OMe, 17·4. $C_7H_{14}O_5$ requires OMe, 17·5%). An *X*-ray diffraction pattern of this material was indistinguishable from that of 3-*O*-methyl-L-rhamnose.

Benzene–ethanol extract of Spruce wood. Spruce-wood sawdust (60 g.) was extracted exhaustively first with benzene–ethanol (2 : 1; v/v) and then with ethanol, and the syrup resulting after removal of the solvents was hydrolysed with boiling N-sulphuric acid for 5 hr. Chromatographic examination of the solution showed that 3-*O*-methyl-L-rhamnose was absent, but traces of xylose and rhamnose were detected.

Examination of fraction D. Paper-chromatogram examination of this fraction showed neutral sugars as well as uronic acids. Accordingly the syrup (12 g.) was shaken with methanolic hydrogen chloride (2% w/v; 300 c.c.) until a test portion of the solution no longer reduced Fehling's solution. The solution was then filtered, after the addition of silver carbonate, and concentrated to a syrup (12 g.). An attempt was made to extract preferentially the methylated uronic acid derivatives from their solution in water with chloroform. There resulted a chloroform-soluble extract (D_1, 3 g.) and a water-soluble sugar fraction (D_2; 9 g.) but no obvious fractionation of the sugars had taken place.

The Isolation of Methylated Uronic Acids from D_1.—The chloroform-soluble extract (D_1; 3 g.) was methylated with sodium hydroxide and methyl sulphate, and the solution extracted continuously with chloroform, first while strongly alkaline and then after acidification with dilute sulphuric acid. The first extract, which consisted of neutral sugars, was discarded. The methylated sugar acids (2 g.), which were obtained on concentration of the second extract, were reduced with a solution of lithium aluminium hydride (1·5 g.) in ether, and the neutral methylated sugars resulting (1 g.) were isolated in the usual manner. When the residual aqueous solution was acidified and again extracted a quantity (0·3 g.) of acids which had escaped reduction was recovered. The neutral fraction (1·0 g.) was further methylated, first with sodium hydroxide and methyl sulphate and then with silver oxide and methyl iodide, and the product (0·75 g.) (Found: OMe, 51·6. Calc. for $C_{18}H_{34}O_{10}$: OMe, 52·9%) was distilled, giving a main fraction (0·62 g.), b. p. 170—175° (bath-temp.)/0·3 mm., n_D^{18} 1·4636, $[\alpha]_D$ +112° ($CHCl_3$).

Hydrolysis of the disaccharide. The syrup (620 mg.) was hydrolysed with boiling N-sulphuric acid (20 c.c.) for 7 hr. The cooled solution was neutralised (barium hydroxide) and filtered, and the filtrate extracted exhaustively with chloroform. Concentration of the extract gave a syrup (580 mg.) which was separated on sheets of filter paper (solvent *c*). There resulted unchanged disaccharide, 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose (95 mg.), $[\alpha]_D$ +81° ($CHCl_3$) {the derived *N*-phenylglycosylamine derivative had m. p. 137°, $[\alpha]_D$ +260° ($COMe_2$)}, and 3 : 4-di-*O*-methyl-D-xylose (100 mg.), $[\alpha]_D$ +40° ($CHCl_3$) (Found: OMe, 36·1. Calc. for $C_7H_{14}O_5$: OMe, 34·8%) (characterised as 3 : 4-di-*O*-methyl-D-xylonolactone, m. p. and mixed m. p. 64°).

Similar examination of fraction *D* showed that it contained 4-*O*-methyl-D-glucuronic acid, D-galacturonic acid, and 2-*O*-(4-*O*-methyl-α-D-glucosidurono)-D-xylose.

The authors thank Professor L. E. Wise and Dr. H. F. Lewis of the Institute of Paper Chemistry, Appleton, Wisconsin, U.S.A., and The Director, Forest Products Research Establishment, Princes Risborough, Bucks, for the gifts of wood samples. They also thank Professor E. L. Hirst, F.R.S., and Dr. S. Dunstan for a specimen of 3-*O*-methyl-L-rhamnose. One of them (A. R. N. G.) thanks the University of Bristol for the award of a Graduate Scholarship.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, BRISTOL 8.
[Present Addresses: A. R. N. G., HANNAH DAIRY RESEARCH INSTITUTE, AYR.
J. K. N. J., QUEEN'S UNIVERSITY, KINGSTON, ONTARIO, CANADA.]

[*Received, January 27th,* 1954.]

Di-tert.-*butylberyllium and Beryllium Hydride.*

By G. E. Coates and F. Glockling.

[Reprint Order No. 5131.]

Di-*tert.*-butylberyllium, prepared from *tert.*-butylmagnesium chloride and beryllium chloride, decomposes rapidly above 100° to give mainly beryllium hydride, BeH_2, and *iso*butene. The hydride, whichis stable up to 240°, forms bisdimethylaminoberyllium with dimethylamine, and beryllium borohydride with diborane, and is slowly hydrolysed by water.

Dimethylberyllium decomposes at an appreciable rate only when heated to 190—200° (Coates, Glockling, and Huck, *J.*, 1952, 4496). Progressive replacement of the hydrogen atoms by methyl groups profoundly affects the thermal stability. Thus diethylberyllium decomposes above about 85° in a complex reaction giving a variety of products (Goubeau and Rodewald, *Z. anorg. Chem.*, 1949, **258**, 162). Replacement of another hydrogen results in still lower thermal stability, since di*iso*propylberyllium (Coates and Glockling, *J.*, 1954, 22) decomposes above 50° in a much cleaner reaction in which *iso*propylberyllium hydride and propene are the main products obtained at 200°. The further pyrolysis of this hydride is complex and results in no well-defined solid products.

The present work describes the final member of this series, di-*tert.*-butylberyllium, which was prepared from *tert.*-butylmagnesium chloride and beryllium chloride in ether. Complete separation from ether was not achieved but, even when combined with 45 mole % of ether, it begins to decompose at about 50°. Material of this composition formed coloured colloidal solutions, from which metallic beryllium slowly separated, when allowed to stand at room temperature for several weeks. Rather surprisingly this was not observed when the ether content had been reduced to 37%, but decomposition was still observed at 40—50°.

Substitution of hydrogen by methyl groups thus causes a progressive decrease in thermal stability in the order: $Me_2Be > (MeCH_2)_2Be > (Me_2CH)_2Be > (Me_3C)_2Be$. In contrast with results obtained with di*iso*propylberyllium no half-hydride ($Me_3C{\cdot}BeH$) was isolated from the thermal decomposition of di-*tert.*-butylberyllium, and the reaction proceeded smoothly to give mainly *iso*butene and beryllium hydride which, however, retained some *tert.*-butyl groups as shown by its formation of a little *iso*butane on hydrolysis: $(Me_3C)_2Be \longrightarrow BeH_2 + 2Me_2C{=}CH_2$. The proportion of *tert.*-butyl groups to hydrogen atoms in the product diminished as the temperature of the pyrolysis was increased. After pyrolysis at 150° the product contained 89 mole % of beryllium hydride and 96% at 210°. Pyrolysis at 240—290° caused increasing liberation of hydrogen which became very rapid at about 300°.

Several properties of beryllium hydride as prepared in this way are in marked contrast to those recorded by Schlesinger *et al.* (*J. Amer. Chem. Soc.*, 1951, **73**, 4585) who obtained it from dimethylberyllium and lithium aluminium hydride in ether. Their product apparently differed from ours mainly in its ether content (89 mole % of beryllium hydride; the remainder was assumed to be ether), and decomposed quite rapidly at 125° giving hydrogen, ether, and ethane. This great difference in thermal stability is very surprising, and we cannot account for it unless it is due to attack on the ether in the manner of organolithium compounds. A further remarkable difference is the behaviour on hydrolysis. Water vapour reacted vigorously with Schlesinger's material even at −196°, but our hydride reacted slowly and incompletely with water at room temperature or 50°, and addition of hydrochloric acid was necessary to complete the hydrolysis. This inertness towards water was most marked with the purest (96 mole %) beryllium hydride.

Beryllium hydride reacted slowly and quantitatively at 155° with dimethylamine, forming hydrogen and the known compound, bisdimethylaminoberyllium $\{Be(NMe_2)_2\}_3$ (Coates and Glockling, *loc. cit.*). Conversion of beryllium hydride into the volatile beryllium borohydride BeB_2H_8 (Burg and Schlesinger, *J. Amer. Chem. Soc.*, 1940, **62**, 3425 (by reaction with diborane at 95° was slow and incomplete, and was complicated by

partial decomposition of the diborane, although sufficient crystalline material was obtained for identification. The thermal stability of beryllium hydride prepared from di-*tert.*-butylberyllium, appears to be only a little less than that of magnesium hydride prepared by the pyrolysis of primary magnesium alkyls (Wiberg and Bauer, *Chem. Ber.*, 1952, **85**, 593). Magnesium hydride is also quite involatile and forms a borohydride with diborane, but in contrast to (our) beryllium hydride it is vigorously hydrolysed by water or methanol. There was no evidence of reaction between trimethylamine and beryllium hydride, even after 6 hrs. with an excess of amine at 210°. The heat of polymerisation of the hydride is apparently too great to allow the depolymerisation which must necessarily precede co-ordination to trimethylamine. Only strong donors like trimethylamine are able to depolymerise dimethylberyllium (Coates and Huck, *J.*, 1952, 4501), and since metal hydrides tend to be more strongly polymerised than metal alkyls (see Coates and Glockling, *loc. cit.*) the failure of trimethylamine to react with beryllium hydride is not very surprising. It is interesting that dimethylmagnesium takes up trimethylamine reversibly, the dissociation pressure being given by $\log_{10} p$ (mm.) $= 11{\cdot}66 - 3316/T$; $\Delta H = 15{\cdot}2$ kcal./mole. Even though combination occurs in this case, no monomeric or volatile compound is formed. Aluminium affords two volatile compounds AlH_3,NMe_3 and $AlH_3,2NMe_3$ (Wiberg, Graf, and Uson, *Z. anorg. Chem.*, 1953, **272**, 221; Stecher and Wiberg, *Ber.*, 1942, **75**, 2002).

Trimethylamine displaces ether from di-*tert.*-butylberyllium, though not completely under the conditions employed. The major product is a crystalline compound, readily volatile and solid at room temperature, which is almost certainly the highly symmetrical di-*tert.*-butylberyllium–trimethylamine $(Me_3C)_2\overset{-}{B}e{\cdot}\overset{+}{N}Me_3$.

Experimental

Di-tert.-*butylberyllium.*—Anhydrous beryllium chloride (8·0 g.) in ether (150 c.c.) was added slowly to a well-stirred solution under nitrogen of *tert.*-butylmagnesium chloride prepared from magnesium (19·2 g.) and *tert.*-butyl chloride (74 g.) in ether (500 c.c.). Stirring was continued for 2 hr. after addition of the beryllium chloride, then most of the ether was removed by pumping at room temperature. High-vacuum distillation of the di-*tert.*-butylberyllium and much ether was accomplished by heating with continuous pumping at 60° for 2 days, then at 75° for 1 day. The product was transferred to a special reflux-distillation flask (Coates and Glockling, *loc. cit.*) by heating at 50° with continuous pumping, leaving a dark residue of metallic appearance. Reflux distillation was carried out for 4 hr. at 35—40°, followed by 4 hr. at room temperature with the condenser cooled to −40°. The material was then distributed between a series of sample tubes as described previously (*idem, ibid.*). It decomposed slowly at room temperature, giving what appeared to be a colloidal solution of beryllium varying in colour from reddish-blue to light brown. Specimens were therefore stored in a vacuum-flask containing some solid carbon dioxide. The residue from the final distillation was a colourless, highly viscous oil (~0·5 c.c.), involatile at room temperature, and unaffected by short exposure to air. It was not investigated further.

Analysis of Di-tert.-*butylberyllium by Hydrolysis.*—The contents of a sample tube (0·1578 g.) were distilled at room temperature (3 hr.) into an evacuated trap cooled in liquid air. After the distillate had been exposed to water vapour for several hours, a large excess of water was condensed in the trap, and the reaction allowed to proceed gently, the trap being cooled occasionally. Finally the water was boiled and an excess of dilute hydrochloric acid condensed on the mixture to complete the hydrolysis. No hydrogen was formed. The gaseous hydrolysis products and excess of water were fractionally condensed in two traps cooled in solid carbon dioxide (−78·5°) in series with two in methylene chloride slush baths (−96°) and a liquid-air trap. Ice in the first trap was melted twice to remove dissolved gases. After 90 min. *iso*-butane (formed by hydrolysis of di-*tert.*-butylberyllium), which had mostly condensed in the ampoule cooled in liquid air, was refractionated in the same manner, as were the contents of the ampoules cooled to −96°, containing mainly ether. The final quantities were: ether (15·8 N-c.c.; v. p. at 0°, 184 mm.) and *iso*butane (39·2 N-c.c., v. p. at −78·5°, 20 mm.), unaffected by dilute aqueous potassium permanganate. Thus the material has the average composition; $(Me_3C)_2Be$, $0{\cdot}806Et_2O$, *i.e.*, 55·4 mole % of di-*tert.*-butylberyllium. A further

analysis, by the same procedure, gave the composition as 57·2 mole % of di-*tert.*-butylberyllium. The beryllium chloride formed by hydrolysis was shown to be free from magnesium by chromatographic absorption of the acetate on Whatman No. 1 paper. Pure magnesium and beryllium acetates were used for comparison, the detecting agent being 8-hydroxyquinoline. The solvent used was acetone (80 parts), acetic acid (2 parts), and water (10 parts, all by volume). The R_F value (0·51—0·69) agreed well with that for pure beryllium acetate (0·53—0·70). The R_F value for magnesium acetate was 0·27—0·38.

Part of the material containing 55·4 mole % of di-*tert.*-butylberyllium was again introduced into the reflux still and analysed after 24 hr.' continuous pumping at room temperature (condenser at −20°). The product then contained 63·3 mole % if di-*tert.*-butylberyllium, the remainder being ether. This preparation remained clear after two months at room temperature.

Beryllium Hydride.—Pyrolysis of di-tert.-*butylberyllium.* (a) *At* 150° : Di-*tert.*-butylberyllium (0·3137 g., consisting of 31·4 N-c.c. of ether + 39·0 N-c.c. di-*tert.*-butylberyllium) was introduced into the high-temperature bulb (Schlesinger and Burg, *J. Amer. Chem. Soc.*, 1937, **59**, 780) and slowly heated. Decomposition became quite rapid at 100°, and at 150° a white apparently non-crystalline solid formed. After 5 hr. at 150° the gaseous products (96·5 N-c.c.), which were completely condensable in liquid air, were separated and the residue was re-heated at 150° for 5 hr. with continuous pumping through a liquid-air trap. The entire gaseous products (100·8 N-c.c.) were fractionally condensed, using the same sequence of traps as in the hydrolysis experiments, giving ether (32·8 N-c.c.; v. p. at 0°, 186 mm.) and *iso*butene (66·8 N-c.c.; v. p. at −78·5°, 23 mm.). The latter was incompletely absorbed when shaken with excess of aqueous potassium permanganate (residual vol., 5 N-c.c.). The two ampoules, cooled to −78·5°, contained 1 N-c.c. of unidentified gas.

The residue was remarkably resistant to hydrolysis; keeping it overnight with excess of water produced only 43 N-c.c. of hydrogen. With dilute hydrochloric acid the total volume of hydrogen produced was 61·5 N-c.c. (completely oxidised by copper oxide at 300°). Fractionation of the condensable gases in the usual manner gave *iso*butane (7·7 N-c.c.) (not absorbed by aqueous potassium permanganate) and ether (~0·4 N-c.c.). The hydrogen and *iso*butane values obtained by hydrolysis thus correspond to 89 mole % of beryllium hydride.

(b) *At* 210° : Di-*tert.*-butylberyllium (0·8114 g. consisting of 81·2 N-c.c. of ether + 101 N-c.c. of di-*tert.*-butylberyllium) was heated at 150° in the high-temperature bulb until no further increase of pressure occurred. Ether and *iso*butene were removed and the temperature was raised slowly. Hydrogen produced was removed at intervals with a Töpler pump. A slight white deposit was formed on the upper parts of the bulb and after 1 hr. at 210° only 1·8 N-c.c. of hydrogen were formed. Hydrolysis of the white residue with water proceeded to only a small extent even on boiling; with excess of 0·1N-hydrochloric acid hydrogen was evolved quite briskly, but without apparent heat evolution. Even in acid solution evolution of hydrogen continued for some hours at room temperature before the solution became quite clear. The volume of hydrogen obtained was 183·4 N-c.c. Fractional condensation of the condensable hydrolysis products gave *iso*butane (5·2 N-c.c.; not absorbed by potassium permanganate) and ether (1·1N-c.c.). The composition thus corresponds to 96·3 mole % of beryllium hydride.

Reaction of Beryllium Hydride with Dimethylamine : Formation of Bisdimethylaminoberyllium. Di-*tert.*-butylberyllium (0·1532 g., consisting of 12·0 N-c.c. of ether + 20·6 N-c.c. of di-*tert.*-butylberyllium) was heated to 150° in the high-temperature bulb, and the gaseous products were separated. The residue was then heated at 200° for 2 hr. with continuous pumping. The total gaseous products (52·6 N-c.c.) were separated by methods already described, giving ether (12·9N-c.c.), *iso*butene (35·9 N-c.c.), and saturated hydrocarbons (3·3N-c.c.). Dimethylamine (75·5N-c.c.) was added to the beryllium hydride and the mixture heated at 160° for 4 hr. The hydrogen formed (23·5 N-c.c.) was separated, and heating continued at 155° for a further 6 hr., the white solid beryllium hydride having then entirely disappeared. The total volume of hydrogen was 33·8 N-c.c., and of condensable gases (excess of dimethylamine and a little *iso*butane) 42·0 N-c.c. The residue in the high-temperature bulb formed colourless well-defined crystals of bisdimethylaminoberyllium, m. p. 94° (cf. Coates and Glockling, *loc. cit.*, who prepared and characterised this compound).

Reaction of Beryllium Hydride with Diborane : Formation of Beryllium Borohydride.—Di-*tert.*-butylberyllium (0·2294 g. containing 18 N-c.c. of ether + 30·9 N-c.c. of di-*tert.*-butylberyllium) was pyrolysed first at 150° and then for 2 hr. at 200°. Diborane (31·1 N-c.c.) was condensed on the hydride, and the mixture heated at 95° for 6 hr. Hydrogen (6·4 N-c.c.), presumably formed by thermal decomposition of diborane, was separated. Beryllium boro-

hydride (~2 N-c.c.; v. p. at 20°, 5 mm.) was isolated by passing the condensable volatile components through a trap at −78°.

Reaction of Ethereal Di-tert.-*butylberyllium with Trimethylamine.*—Di-*tert.*-butylberyllium (20·8 N-c.c. of ether + 35·7 N-c.c. of di-*tert.*-butylberyllium) was allowed to stand overnight with trimethylamine (108·5 N-c.c.). Volatile products were separated with the container cooled to −20°. Ether was separated from the gaseous mixture by passing it through traps cooled to −95°, and the trimethylamine returned to the reaction vessel. This procedure was twice repeated with heating at 40° for 4 hr. Fractional condensation and absorption of excess of trimethylamine in acid gave ether (18·4 N-c.c.), *iso*butene (3·5 N-c.c.), and excess of trimethylamine (90·1 N-c.c.). Hence 18·4 c.c. of trimethylamine were combined. The inhomogeneous residue consisted of a colourless liquid (probably unused di-*tert.*-butylberyllium and its ether complex) and a colourless crystalline solid of m. p. 42—47°, which is considered to be di-*tert.*-butylberyllium–trimethylamine. Both the solid and the liquid component were fairly volatile at room temperature and could not be separated. Hydrolysis of the mixture with dilute hydrochloric acid gave ether (3·1 N-c.c.) and *iso*butane (63·9 N-c.c.). In spite of various attempts this reaction could not be made to go to completion with displacement of all the ether.

UNIVERSITY OF BRISTOL.
Present addresses: (G. E. C.) UNIVERSITY OF DURHAM;
(F. G.) UNIVERSITY OF LIVERPOOL.

[*Received, February 17th*, 1954.]

The Synthesis and Reactions of Branched-chain Hydrocarbons. Part III. α-Hydroxy-ketones with Secondary and Tertiary Alkyl Groups.*

By W. J. HICKINBOTTOM, A. A. HYATT, and M. B. SPARKE.

[Reprint Order No. 5166.]

Six branched-chain aliphatic ketones are converted by sodium acetylide in liquid ammonia into alk-1-yn-3-ols. Of these, three are hydrated smoothly and in good yield to the unrearranged ketols. Unsaturated ketone was formed as a by-product from a fourth alk-1-yn-3-ol; from another it constituted the sole product. One of the acetylenic alcohols resisted hydration.

THE work described in this paper explores the limitations of a synthesis of α-hydroxy-ketones by the following scheme when R or R′, or both, is a tertiary or secondary alkyl group:

$$\underset{\text{(I)}}{RR'CO} \longrightarrow \underset{\text{(II)}}{RR'C(OH)\cdot C{:}CH} \longrightarrow \underset{\text{(III)}}{RR'C(OH)\cdot CO\cdot CH_3}$$

Good yields of the acetylenic alcohol (II) are obtained when the following ketones (I) react with sodium acetylide in liquid ammonia; pinacolone (R = Me, R′ = CMe_3); 4 : 4-dimethylpentan-2-one (R = Me, R′ = $CMe_3\cdot CH_2\cdot$); pentamethylacetone (R = Pr^i, R′ = Bu^t); hexamethylacetone (R = R′ = Bu^t); di*iso*propyl ketone (R = R′ = Pr^i). In view of the smooth reaction of hexamethylacetone, it was unexpected that methyl triptyl ketone (R = Me, R′ = $CMe_3\cdot CMe_2\cdot$) should be indifferent to sodium acetylide or lithium acetylide in liquid ammonia or in boiling ether or benzene. It is important that if the quaternary carbon atoms of methyl triptyl ketone are separated by a methylene group, as in 3 : 3 : 5 : 5-tetramethylhexan-2-one (R = Me, R′ = $CMe_3\cdot CH_2\cdot CMe_2\cdot$) the acetylenic alcohol can be prepared although only in diminished yield and with some difficulty.

Hydration with boiling 20% aqueous sulphuric acid containing mercuric sulphate gave good yields of the α-hydroxy-ketones (III) from 3 : 4 : 4-trimethylpent-1-yn-3-ol (II; R = Bu^t, R′ = Me), 3 : 5 : 5-trimethylhex-1-yn-3-ol (II; R = $CMe_3\cdot CH_2\cdot$, R′ = Me), and 3 : 4 : 4 : 6 : 6-pentamethylhept-1-yn-3-ol (II; R = $CMe_3\cdot CH_2\cdot CMe_2\cdot$, R′ = Me). Hydration is sluggish if R and R′ are branched. Thus 4-methyl-3-*iso*propylpent-1-yn-3-ol (II; R = R′ = Pr^i) gives only a 40—50% yield of α-hydroxy-ketone. No ketol is formed from 4 : 4-dimethyl-3-*iso*propylpent-1-yn-3-ol: after prolonged boiling, a considerable

* Part II, *J.*, 1951, 3344.

proportion of the alcohol was recovered unchanged and an unsaturated carbonyl compound was formed in poor yield. The alcohol (II; R = R′ = Bu^t) was unchanged by a boiling solution of mercuric sulphate in 20% sulphuric acid or aqueous methanol; similar resistance to hydration has been observed with 2 : 2 : 5 : 5-tetramethylhex-3-yne (Hennion and Banigan, *J. Amer. Chem. Soc.*, 1946, **68**, 1202).

It was established that no rearrangement of the ketol occurred in the hydration of the acetylenic alcohols by reduction to a glycol and identification of the products of oxidative fission of this, and confirmation is afforded by a study of the reaction of the ketols with lithium alkyls.

In the hydration of some acetylenic alcohols, limited elimination of acetylene occurred, generally accompanied by formation of unsaturated carbonylic compounds. These are αβ-unsaturated ketones corresponding to the dehydration product of the normal hydroxy-ketone and have been identified by comparison with authentic specimens from other sources or by ozonolysis. Exceptionally 4 : 4-dimethyl-3-*iso*propylpent-1-yn-3-ol, on attempted hydration, gave 4 : 4-dimethyl-3-*iso*propylpent-2-en-1-al as the main product although only in relatively poor yield.

The isolation of β-*tert.*-butylbutyrolactone in small yield from the products of the hydration of 3 : 4 : 4-trimethylpent-1-yn-3-ol suggests that in this case an unsaturated aldehyde is also formed and then oxidised to the corresponding αβ-unsaturated acid which is known to give the lactone in hot aqueous sulphuric acid.

Experimental

Preparation of 3-*Hydroxy*-3 : 4 : 4-*trimethylpentan*-2-*one* (III; R = Bu^t, R′ = Me).—3 : 4 : 4-*Trimethylpent*-1-*yn*-3-*ol*. Pinacolone (*tert.*-butyl methyl ketone) (340 g.) was added, during 3 hr., to sodium acetylide (from sodium, 85 g.) in liquid ammonia (2 l.). The mixture was stirred at −35° for a further 2½ hr., ammonium chloride (220 g.) was then added, and the ammonia allowed to evaporate overnight. Steam-distillation followed by efficient fractionation gave 3 : 4 : 4-trimethylpent-1-yn-3-ol (310 g.), b. p. 142—144°, n_D^{20} 1·4440, d_{20}^{20} 0·868 (Wouseng *Ann. Chim.*, 1924, **1**, 343, gives b. p. 144°, n_D^{11} 1·4441, d_4^{11} 0·8806), and a small solid residue, presumably 2 : 2 : 3 : 6 : 7 : 7-hexamethyloct-4-yne-3 : 6-diol (Wouseng, *loc. cit.*).

Pinacolone (20 g.) and ethynylmagnesium bromide gave 4 g. of the required alcohol and 3 g. of the diol. From sodium acetylide and pinacolone in ether (Wouseng, *loc. cit.*), the yield of alcohol was 24%; it was higher in boiling ether, but the product also contained 2 : 2 : 5 : 6 : 6-pentamethylhept-4-en-3-one (Hickinbottom and Schlüchterer, *Nature*, 1945, **155**, 19). Potassium acetylide in diethylaniline also gave a poor yield of the required product (Distillers Co. Ltd., B.P. 589,350).

The pinacolone required was prepared (*a*) by rearrangement of pinacol hydrate (Hill and Flosdorf. *Org. Synth.*, Coll. Vol., I, 2nd Edn., p. 462) in 68% yield, and (*b*) from acetic anhydride and *tert.*-butylmagnesium chloride at −50° (Newman and Smith, *J. Org. Chem.*, 1948, **13**, 592) in 61% yield. Reaction of *tert.*-butylmagnesium chloride with acetyl chloride gave yields averaging 15% (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1933, **55**, 1564; 1938, **60**, 2900).

3-*Hydroxy*-3 : 4 : 4-*trimethylpentan*-2-*one* (III; R = Bu^t, R′ = Me). 3 : 4 : 4-Trimethylpent-1-yn-3-ol (126 g.) was added during 2 hr. to boiling 20% sulphuric acid (300 c.c.) in which were dissolved 10 g. of mercuric oxide. The hydration was completed by a further 2 hours' boiling, and the product was removed by steam-distillation. Distillation of the oil so obtained gave 3-hydroxy-3 : 4 : 4-trimethylpentan-2-one (80%), b. p. 174—176°/760 mm., 75—77°/19 mm., n_D^{20} 1·4410, d_{20}^{20} 0·9331 (Locquin and Wouseng, *Compt. rend.*, 1923, **176**, 517, give b. p. 177°, n_D^{11} 1·4442, d_{11}^{11} 0·9388), fraction (*A*) (15 g.), b. p. 160—174°, and a solid (*B*) (1·5 g.), not easily volatile in steam.

3-Hydroxy-3 : 4 : 4-trimethylpentan-2-one was characterised as its semicarbazone, m. p. 194° (Found: C, 53·9; H, 9·35; N, 21·0. Calc. for $C_9H_{19}O_2N_3$: C, 53·7; H, 9·5; N, 20·9%) (Locquin and Wouseng, *loc. cit.*, give m. p. 193—194°). With 2 : 4-dinitrophenylhydrazine it gave a *compound* presumably a pyrazoline, as bright red needles (from glacial acetic acid), m. p. 232°, insoluble in ethanol, ether, or light petroleum, but soluble in benzene or acetic acid (Found: C, 54·9; H, 6·0; N, 18·4. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%).

3-Hydroxy-3 : 4 : 4-trimethylpentan-2-one (12 g.) was reduced by lithium aluminium hydride (5 g.) in ether (110 c.c.) at room temperature for 2 hr., then refluxed for 1 hr., and poured on ice. The precipitated hydroxide was dissolved in dilute hydrochloric acid. The material

extracted by ether yielded pure **3 : 4 : 4-*trimethylpentane*-2 : 3-*diol*** [10·5 g., after crystallisation from light petroleum (b. p. 40—60°)], m. p. 95—96°, b. p. 96°/18 mm. (Found : C, 65·8, 66·0; H, 12·65, 12·4. $C_8H_{18}O_2$ requires C, 65·7; H, 12·4%). This glycol (2·0 g.), methyl alcohol (3 c.c.), water (10 c.c.), and periodic acid (1·0 g.) were shaken together for 4 hr. at room temperature; air was then drawn through the solution into 2 : 4-dinitrophenylhydrazine in aqueous-alcoholic hydrochloric acid. Acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 168°, separated from this solution overnight after warming. The remaining aqueous solution was extracted with ether; the material in this extract gave *tert.*-butyl methyl ketone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126° (after chromatography on alumina).

The lower-boiling fractions (*A*) (above) from a number of hydrations were combined (69 g.) and resolved by fractionation into pinacolone, b. p. 103—107°, n_D^{20} 1·3965—1·3969 (9·1 g.), 3-*tert.*-butylbut-3-en-2-one, b. p. 141—144°, n_D^{20} 1·4339—1·4342 (43 g.), and 3-hydroxy-3 : 4 : 4-trimethylpentan-2-one, b. p. 168—175·5°, n_D^{20} 1·4398—1·4402 (8·2 g.). Redistillation of the second fraction gave the pure ketone, b. p. 142—143°, n_D^{20} 1·4340 (Found : C, 75·9; H, 11·3. Calc. for $C_8H_{14}O$: C, 76·2; H, 11·2%) [semicarbazone, m. p. 165° (Found : C, 58·8; H, 9·3; N, 22·8. Calc. for $C_9H_{17}ON_3$: C, 59·0; H, 9·4; N, 22·9%); 2 : 4-*dinitrophenylhydrazone*, orange yellow, m. p. 116° (Found : C, 55·4; H, 6·1; N, 18·2. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%)]. Favorskaya (*J. Gen. Chem. U.S.S.R.*, 1949, **19**, 2051) gives 3-*tert.*-butylbut-3-en-2-one, b. p. 80—81°/110 mm. (semicarbazone, m. p. 163—164°). Ozonolysis of this ketone gave formaldehyde and a 1 : 2-diketone, which on reduction by lithium aluminium hydride gave a glycol, m. p. 52° (from light petroleum), oxidised by periodic acid to trimethylacetaldehyde and acetaldehyde (Favorski, *J. Russ. Phys. Chem. Soc.*, 1928, **60**, 386, gives m. p. 54° for the glycol). With lithium aluminium hydride in ether the ketone gave 3-tert.-*butylbut*-3-*en*-2-*ol*, b. p. 148°, n_D^{20} 1·4418 (Found : C, 74·8; H, 12·5. $C_8H_{16}O$ requires C, 74·9; H, 12·6%) [**3 : 5**-*dinitrobenzoate*, m. p. 104° (Found : C, 55·9; H, 5·6; N, 9·0. $C_{15}H_{18}O_6N_2$ requires C, 55·9; H, 5·6; N, 8·7%].

The solid (*B*) (above) was sparingly soluble in ether or alcohol, but, crystallised from light petroleum (b. p. 80—100°), had m. p. 98·5° (Found : C, 67·0; H, 9·85; active H, 0. Calc. for $C_8H_{14}O_2$: C, 67·55; H, 9·9%). It is soluble in aqueous alkali and acidification of the aqueous solution precipitated **2 : 3 : 3**-trimethylbut-1-ene-1-carboxylic acid, m. p. 85° (Found : C, 67·8; H, 9·9. Calc. for $C_8H_{14}O_2$: C, 67·55; H, 9·9%), converted into the original lactone by boiling 50% aqueous sulphuric acid. Locquin and Wouseng (*Compt. rend.*, 1924, **174**, 1713) give β-*tert.*-butylbutyrolactone, m. p. 97—98°, and 2 : 3 : 3-trimethylbut-1-ene-1-carboxylic acid, m. p. 85—86°. Petschnikow (*J. pr. Chem.*, 1902, **65**, 178) gives m. p. 96—98° for the lactone.

Preparation of **3-*Hydroxy*-3 : 5 : 5-*trimethylhexan*-2-*one*** (III; R = $Me_3C{\cdot}CH_2$, R′ = Me).—**3 : 5 : 5-*Trimethylhex*-1-*yn*-3-*ol***. Methyl *neo*pentyl ketone (378 g.) with sodium acetylide in liquid ammonia gave **3 : 5 : 5-*trimethylhex*-1-*yn*-3-*ol*** (72%), b. p. 159—161°, n_D^{20} 1·4418, d_{20}^{20} 0·8556 (Found : C, 77·4; H, 11·8. $C_9H_{16}O$ requires C, 77·1; H, 11·5%). The ketone was prepared by the oxidation of di*iso*butylene in 40% yield (Byers and Hickinbottom, *J.*, 1948, 1336; Mosher and Cox, *J. Amer. Chem. Soc.*, 1950, **72**, 3701), or of 4 : 4-dimethylpentan-2-ol with dichromate and aqueous sulphuric acid.

3-*Hydroxy*-3 : 5 : 5-*trimethylhexan*-2-*one*. This *ketol* was obtained in 90% yield by the hydration of **3 : 5 : 5**-trimethylhex-1-yn-3-ol with boiling 20% aqueous sulphuric acid containing mercuric sulphate. It had b. p. 75°/16 mm., n_D^{20} 1·4354, d_{18}^{18} 0·9152 (Found : C, 68·25; H, 11·3. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%), and gave a *semicarbazone*, m. p. 160°, very soluble in alcohol (Found : C, 55·6; H, 9·5; N, 19·8. $C_{10}H_{21}O_2N_3$ requires C, 55·8; H, 9·8; N, 19·5%), a 2 : 4-*dinitrophenylhydrazone*, m. p. 114°, light yellow-orange crystals from aqueous alcohol (Found : C, 53·4; H, 6·9; N, 16·9. $C_{15}H_{22}O_5N_4$ requires C, 53·2; H, 6·5; N, 16·6%), and, in hot aqueous sulphuric acid, a 2 : 4-*dinitrophenylpyrazoline*, m. p. 161°, orange-red needles (Found : C, 56·0; H, 6·9; N, 17·4. $C_{15}H_{20}O_4N_4$ requires C, 56·2; H, 6·3; N, 17·5%).

Reduction of the ketol in ether by lithium aluminium hydride gave **3 : 5 : 5-*trimethylhexane*-2 : 3-*diol***, a viscous liquid of faint odour, b. p. 95—96°/12 mm., n_D^{20} 1·4531, d_{17}^{17} 0·9352 (Found : C, 67·0, 67·4; H, 12·2, 12·4. $C_9H_{20}O_2$ requires C, 67·4; H, 12·6%), which with periodic acid in aqueous methanol gave acetaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 168—169°) and methyl *neo*pentyl ketone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 100—101°).

Preparation of **3-*Hydroxy*-3 : 4 : 4 : 6 : 6-*pentamethylheptan*-2-*one*** (III; R = $Me_3C{\cdot}CH_2{\cdot}CMe_2$, R = Me).—**3 : 4 : 4 : 6 : 6-*Pentamethylhept*-1-*yn*-3-*ol***. 3 : 3 : 5 : 5-Tetramethylhexan-2-one (312 g.) was added dropwise to sodium acetylide (from 46 g. of sodium) in anhydrous ammonia (3 l.).

After 3½ hr. an excess of ammonium chloride was added and the ammonia allowed to evaporate. Steam-distillation of the residue gave about equal amounts of unchanged 3 : 3 : 5 : 5-tetramethylhexan-2-one and 3 : 4 : 4 : 6 : 6-*pentamethylhept*-1-*yn*-3-*ol*, b. p. 90/10 mm., n_D^{20} 1·4613, d_{20}^{20} 0·8842 (Found : C, 78·85; H, 12·15. $C_{12}H_{22}O$ requires C, 79·05; H, 12·15%). A satisfactory yield requires use of very efficient stirring and an excess of ammonia.

3-*Hydroxy*-3 : 4 : 4 : 6 : 6-*pentamethylheptan*-2-*one*. Hydration of the foregoing alcohol (273 g.) as in other preparations gave the required *ketol* (270 g.), b. p. 85—88/2 mm. This solidified but was too soluble in organic solvents to be recrystallised economically, and was obtained pure by washing with small quantities of ice-cold light petroleum (b. p. 40—60°), then forming waxy white crystals, m. p. 42—43°, b. p. 88°/2 mm. [Found : C, 72·1; H, 11·9; active H, 0·5%; *M* (Rast), 187. $C_{12}H_{24}O_2$ requires C, 71·9; H, 12·1; active H, 0·5%; *M*, 200]. No derivatives could be obtained.

Preparation of 3-*Hydroxy*-4-*methyl*-3-iso*propylpentan*-2-*one* (III; R = R′ = Pr^i).—4-*Methyl*-3-iso*propylpent*-1-*yn*-3-*ol*. Reaction of di*iso*propyl ketone (684 g.) with sodium acetylide in liquid ammonia gave the required alcohol (793 g.), b. p. 162—164°/760 mm., n_D^{20} 1·4470, d_{23}^{23} 0·8675 (Thompson, Burr, and Shaw, *J. Amer. Chem. Soc.*, 1941, **63**, 186, give b. p. 162—164°, n_D^{20} 1·4492), and 2 : 7-dimethyl-3 : 6-di*iso*propyloct-1-yne-3 : 6-diol (2·5 g.), m. p. and mixed m. p. 108—109° (Iotsitch, *Bull. Soc. chim.*, 1908, **4**, 1203, gives m. p. 106—107°).

3-*Hydroxy*-4-*methyl*-3-iso*propylpentan*-2-*one*. Hydration of 4-methyl-3-*iso*propylpent-1-yn-3-ol (560 g.) as above yielded the required ketol (246 g.), together with 4-methyl-3-*iso*propylpent-3-en-2-one, unchanged acetylenic alcohol, and 3-*methyl*-2-iso*propylbut*-1-*ene*-1-*carboxylic acid*, m. p. 127·5° (3 g.) [Found : C, 69·6; H, 10·3; active H, 0·59%; *M* (Rast), 162. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3; active H, 0·64%; *M*, 156]. Attempts to prepare a lactone from the acid by warming it with 80% sulphuric acid were unsuccessful. Ozonolysis of the acid in chloroform gave di*iso*propyl ketone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 95°). By further hydration the lower-boiling fractions gave pure unsaturated ketone (110 g.), the ketol (51 g.), the unsaturated acid (2·2 g.), and di*iso*propyl ketone (10 g.).

The unsaturated ketone, b. p. 67·5°/17·5 mm., n_D^{20} 1·4450 (Found : C, 77·1; H, 11·7. $C_9H_{16}O$ requires C, 77·1; H, 11·5%), is identical with that obtained by the rearrangement of 4-methyl-3-*iso*propylpent-1-yn-3-ol with formic acid. It gave no semicarbazone or 2 : 4-dinitrophenylhydrazone. Reduction by lithium aluminium hydride in ether gave 4-*methyl*-3-iso*propylpent*-3-*en*-2-*ol*, b. p. 77—78°/14 mm., n_D^{20} 1·4591 (Found : C, 76·3; H, 12·6. $C_9H_{18}O$ requires C, 76·0; H, 12·8%) [3 : 5-*dinitrobenzoate*, m. p. 94°, white needles from light petroleum (b. p. 60—80°) (Found : C, 57·4; H, 6·1; N, 8·5. $C_{16}H_{20}O_6N_2$ requires C, 57·1; H, 6·0; N, 8·3%)]. The unsaturated ketone was identified by ozonolysis in chloroform to acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126°) and a substance which was reduced by lithium aluminium hydride in ether to a glycol, m. p. 48°. This glycol with periodic acid in aqueous methanol gave acetaldehyde and *iso*butaldehyde (2 : 4-dinitrophenylhydrazones, m. p.s and mixed m. p.s 165° and 187° respectively). The glycol is therefore 2-methylpentane-3 : 4-diol (Umnova, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 1541, gives m. p. 48—49°).

Pure 3-*hydroxy*-4-*methyl*-3-iso*propylpentan*-2-*one* is a colourless liquid of ketonic odour, b. p. 85°/20 mm., n_D^{20} 1·4410, d_{23}^{23} 0·9242 (Found : C, 68·6; H, 11·8. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%). No semicarbazone or 2 : 4-dinitrophenylhydrazone could be prepared from it. It is reduced by lithium aluminium hydride in ether to 4-*methyl*-3-iso*propylpentane*-2 : 3-*diol*, m. p. 51—52°, b. p. 111°/18 mm. (Found : C, 68·0; H, 12·7. $C_9H_{20}O_2$ requires C, 67·45; H, 12·6%), oxidised by periodic acid in aqueous methanol to di*iso*propyl ketone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 96°) and acetaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 168°).

Attempted Preparation of 3-*Hydroxy*-4 : 4-*dimethyl*-3-iso*propylpentan*-2-*one*.—4 : 4-*Dimethyl*-3-iso*propylpent*-1-*yn*-3-*ol* (I; R = Bu^t, R′ = Pr^i). Pentamethylacetone (269 g.) and sodium acetylide (from 60 g. of sodium) in liquid ammonia (2 l.) gave 4 : 4-*dimethyl*-3-iso*propylpent*-1-*yn*-3-*ol* (265 g.), b. p. 65—68°/16 mm. Distillation through a highly efficient column gave the pure *alcohol* as a mobile colourless liquid of powerful odour, b. p. 174·5—176·0°, n_D^{20} 1·4421—1·4423, d_{20}^{20} 0·8758 (Found : C, 77·65; H, 12·0. $C_{10}H_{18}O$ requires C, 77·85; H, 11·8%).

Attempts to hydrate the alcohol by mercuric sulphate in hot aqueous methanol (Thomas, Campbell, and Hennion, *J. Amer. Chem. Soc.*, 1938, **60**, 718) gave only unchanged alcohol. Even when the alcohol (170 g.) was boiled with 20% sulphuric acid containing mercuric sulphate for 10 hr., a considerable amount was recovered unchanged, but there was a fraction (20·5 g.), b. p. 78—85°/25 mm., n_D^{20} 1·4670—1·4690, consisting essentially of 4 : 4-*dimethyl*-3-iso*propylpent*-2-*enal*, and a high-boiling residue (0·5 g.) which solidified and could not be recrystallised

(Found : *M*, 195; active H, 0·58. Calc. for $C_{10}H_{18}O_2$ corresponding to the acid : *M*, 170; active H, 0·59%). The pentenal had b. p. 98°/18 mm., n_D^{20} 1·4689 (Found : C, 77·45; H, 11·7. $C_{10}H_{18}O$ requires C, 77·85; H, 11·8%), and gave a *semicarbazone*, m. p. 208° (Found : C, 62·6; H, 9·9; N, 19·8. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·0; N, 19·9%), and 2 : 4-*dinitrophenylhydrazone*, red needles (from 50% acetic acid), m. p. 200·5° not depressed on admixture with the dinitrophenylhydrazone of 4 : 4-dimethyl-3-*iso*propylpent-2-enal obtained by rearrangement of 4 : 4-dimethyl-3-*iso*propylpent-1-yn-3-ol with formic acid (J. Hancock, personal communication) (Found : C, 57·75; H, 6·75; N, 16·5. $C_{16}H_{22}O_4N_4$ requires C, 57·45; H, 6·65; N, 16·75%). It is reduced by lithium aluminium hydride in ether to the corresponding *alcohol*, b. p. 91°/13 mm., n_D^{20} 1·4623 (Found : C, 76·75; H, 12·95. $C_{10}H_{20}O$ requires C, 76·85; H, 12·9%).

Preparation of 3-tert.-*Butyl*-4 : 4-*dimethylpent*-1-*yn*-3-*ol*.—Hexamethylacetone (45 g.) was added dropwise to a well-stirred suspension of sodium acetylide (from 10 g. of sodium) in liquid ammonia (800 c.c.). Stirring was continued for 3 hr., then the mixture was decomposed by ammonium chloride. After the ammonia had evaporated the product was steam-distilled to remove 3-tert.-*butyl*-4 : 4-*dimethylpent*-1-*yn*-3-*ol* (36 g.), a colourless mobile liquid with a powerful odour, b. p. 74—75°/14 mm., n_D^{20} 1·4589, d_{23}^{23} 0·8825 (Found : C, 78·8, 78·35; H, 12·35, 12·05. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). A small amount of solid material was also obtained (0·5 g.), having m. p. 151° after crystallisation from light petroleum (b. p. 60—80°). It was identified as 3 : 6-di-*tert.*-butyl-2 : 2 : 7 : 7-tetramethyloct-4-yne-3 : 6-diol by comparison (m. p. and mixed m. p.) with an authentic specimen prepared by the following method.

3-*tert.*-Butyl-4 : 4-dimethylpent-1-yn-3-ol (2 g.) was added to sodamide (from 0·5 g. of sodium) n anhydrous ammonia (10 c.c.). After 2 hours' stirring hexamethylacetone (1·5 g.) was added, and stirring continued for another 2 hr. Ammonium chloride was then added, the ammonia allowed to evaporate, and the residue extracted with ether (Soxhlet). Evaporation of the extract left 3 : 6-*di*-tert.-*butyl*-2 : 2 : 6 : 7-*tetramethyloct*-4-*yne*-3 : 6-*diol*, a white volatile crystalline solid, m. p. 152—154° after crystallisation from light petroleum (b. p. 60—80°) (Found : C, 76·95; H, 12·1. $C_{20}H_{38}O_2$ requires C, 77·35; H, 12·35%).

Prolonged heating with 20% aqueous sulphuric acid containing mercuric sulphate or with aqueous methanol containing mercuric sulphate failed to bring about any detectable hydration of 3-*tert.*-butyl-4 : 4-dimethylpent-1-yn-3-ol : it was recovered unchanged.

With respect to this and the following paper the authors are indebted to the Research Group of the Institute of Petroleum for grants, and to the Department of Scientific and Industrial Research for a maintenance grant (to M. B. S.).

UNIVERSITY OF LONDON, QUEEN MARY COLLEGE,
MILE END ROAD, LONDON, E.1. [*Received, February 27th*, 1954.]

The Synthesis and Reactions of Branched-chain Hydrocarbons. Part IV. The Synthesis of Ketones with Quaternary Carbon Atoms.*

By W. J. HICKINBOTTOM, A. A. HYATT, and M. B. SPARKE.

[Reprint Order No. 5167.]

The rearrangement of some ditertiary glycols in concentrated sulphuric acid has been examined as a possible route to ketones having two or more quaternary carbon atoms. It is accompanied by varying amounts of fission into olefins and ketones.

The preparation of glycols from hydroxy-ketones has been improved by using lithium alkyls instead of alkylmagnesium halides.

A POSSIBLE synthesis of hydrocarbons with two or more quaternary carbon atoms involves rearrangement of ditertiary glycols (I) to ketones (II or III), followed by reduction of the carbonyl group. The reduction will form the subject of a subsequent paper : an investigation of the rearrangement is now reported, with the object of determining its usefulness.

Preparation of the glycols (I) by reaction of α-hydroxy-ketones (IV) with methylmagnesium halides is unsatisfactory both in yield and in ease of reaction. A considerable

* Part III, preceding paper.

improvement in yield is obtained by use of methyl-lithium, more particularly if the solution is concentrated by distillation.

Rearrangement of 2 : 3 : 4 : 4-tetramethylpentane-2 : 3-diol (I*b*; R = Bu^t) in cold concentrated sulphuric acid gave 3 : 3 : 4 : 4-tetramethylpentan-2-one (III*b*; R = Bu^t) and some hexamethylacetone (II*b*; R = Bu^t). 2 : 3 : 5 : 5-Tetramethylhexane-2 : 3-diol

(*a*) HO·CR$_2$·CMe$_2$·OH	R·CO·CRMe$_2$	CR$_2$Me·COMe	HO·CR$_2$·COMe
(*b*) HO·CRMe·CMe$_2$·OH	R·CO·CMe$_3$	CRMe$_2$·COMe	HO·CRMe·COMe
(I)	(II)	(III)	(IV)

(I*b*; R = CMe$_3$·CH$_2$) yielded under similar conditions 3 : 3 : 5 : 5-tetramethylhexan-2-one (III*b*; R = CMe$_3$·CH$_2$) and a small amount of 2 : 2 : 5 : 5-tetramethylhexan-3-one (II*b*; R = CMe$_3$·CH$_2$). In both these rearrangements there was evidence of the formation of olefin and a lower-boiling ketone, but the amounts were too small to permit accurate identification. The formation of fission products was noticeably greater during the rearrangement of 2 : 4-dimethyl-3-*iso*propylpentane-2 : 3-diol (I*a*; R = Pr^i); acetone corresponding to not more than 4% fission of the glycol was isolated as well as some olefin which could not be precisely identified. The normal products of the rearrangement, 2 : 4 : 4 : 5-tetramethylhexan-3-one (II*a*; R = Pr^i) and 2 : 3-dimethyl-3-*iso*propylpentan-4-one (III*a*; R = Pr^i), were obtained in good yield.

No rearrangement products were obtained by the action of cold sulphuric acid on 2 : 3 : 4 : 4 : 6 : 6-hexamethylheptane-2 : 3-diol (I*b*; R = CMe$_3$·CH$_2$·CMe$_2$). Instead, methyl *iso*propyl ketone and a mixture of olefins were obtained. The yield of pure ketone indicates 50% of fission as a minimum while calculations from the yield of crude olefin suggest a much higher figure. Discussion of the factors which may determine the course of the reaction is reserved for a later paper.

Experimental

Preparation of Glycols.—The conditions described by Locquin and Wouseng (*Compt. rend.*, 1923, **176**, 682; cf. Leers, *Bull. Soc. chim.*, 1926, **39**, 423) gave yields of about 20%. Use of methyl-lithium was more satisfactory.

3-Hydroxy-3 : 4 : 4-trimethylpentan-2-one (38 g.) in ether (100 c.c.) was added to a stirred solution of methyl-lithium (from 9 g. of lithium, 115 g. of methyl iodide, and 600 c.c. of ether) at 0°. Reaction was completed by 2 hours' stirring at room temperature and 6 hours' refluxing. The mixture was poured into dilute acetic acid and ice, and extracted with ether. The extracts were washed with aqueous sodium carbonate and sodium thiosulphate, dried, and distilled. 2 : 3 : 4 : 4-Tetramethylpentane-2 : 3-diol had b. p. 98—100°/17 mm., m. p. 22°, n_D^{20} 1·4597 (supercooled) (yield 24·5 g., 58%). Locquin and Wouseng (*loc. cit.*) give b. p. 99—100°/13 mm., melting in the hand. Fission of the glycol by periodic acid and separation of the products by the method described on p. 2535 gave acetone and pinacolone, identified by comparison of their 2 : 4-dinitrophenylhydrazones with genuine specimens.

The following glycols were prepared by adding 3-hydroxy-3 : 4 : 4-trimethylpentan-2-one to the appropriate alkyl-lithium in ether, replacing the solvent by benzene, and heating under reflux: 2 : 2 : 3 : 4-*Tetramethylhexane*-3 : 4-*diol* (25%), m. p. 29°, b. p. 109°/17 mm. (Found: C, 69·2; H, 12·6. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·7%). 2 : 2 : 3 : 4 : 5-*Pentamethylhexane*-3 : 4-*diol* (31%), m. p. 50°, b. p. 103—104°/3 mm. (Found: C, 70·4; H, 12·6. $C_{11}H_{24}O_2$ requires C, 70·2; H, 12·8%). 2 : 2 : 3 : 4-*Tetramethyloctane*-3 : 4-*diol* (20%), m. p. 59°, b. p. 94/2 mm. (Found: C, 71·2; H, 12·65. $C_{12}H_{26}O_2$ requires C, 71·2; H, 12·95%). Each of these glycols was oxidised by periodic acid in aqueous methanol to pinacolone and a ketone corresponding to the structure of the glycol. They were converted into 2 : 4-dinitrophenylhydrazones which were separated by chromatography on silica.

Preparation of other glycols is described below.

Rearrangement of 2 : 3 : 4 : 4-*Tetramethylpentane*-2 : 3-*diol.*—The diol (190 g.) was added slowly to concentrated sulphuric acid (2100 g.) at −10°, with efficient stirring. Next morning, the solution was poured on crushed ice (3 kg.) and steam-distilled. The yellow volatile oil was separated, dried, and resolved by precise distillation into 3 : 3 : 4 : 4-tetramethylpentan-2-one, b. p. 165—168° (117 g.), which solidified, and fractions containing hexamethylacetone. After draining on porous earthenware and crystallising from light petroleum, 3 : 3 : 4 : 4-tetramethylpentan-2-one had m. p. 62°, b. p. 168° (semicarbazone, m. p. 207—208°). Locquin and

Wouseng (*ibid.*, 1924, **35**, 753) give m. p. 63—64°, b. p. 167·4° (semicarbazone, m. p. 207—208°). The 2 : 4-dinitrophenylhydrazone formed orange needles, m. p. 188·5° (Found : C, 56·0; H, 7·1; N, 17·8. Calc. for $C_{15}H_{22}O_4N_4$: C, 55·9; H, 6·9; N, 17·4%) (Howard *et al.*, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 365, give m. p. 182—183°).

Preparation and Rearrangement of 2 : 3 : 5 : 5-*Tetramethylhexane*-2 : 3-*diol*.—3-Hydroxy-3 : 5 : 5-trimethylhexan-2-one (190 g.) in ether was added slowly to methyl-lithium [from lithium (42 g.) and methyl bromide in ether (2600 c.c.)] at room temperature. The bulk of the ether (2000 ml.) was then distilled off and the concentrated residue heated under reflux for 10 hr., then decomposed by water. The *glycol*, removed by extraction with ether and distilled, had m. p. 39°, b. p. 100°/13·5 mm., n_D^{20} 1·4538 (supercooled) (Found : C, 68·7; H, 12·8. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·75%). The yield was 90%, but about 60% if concentration of the ethereal reaction mixture was omitted.

Fission of the glycol into acetone and 4 : 4-dimethylpentan-2-one was brought about by shaking a solution of the glycol (2 g.) in methanol (7 c.c.) and water (12 c.c.) with periodic acid (1·5 g.). A yellow oil separated when the solution was diluted after 4 hr.; it consisted of a mixture of two ketones which were separated by chromatography of their 2 : 4-dinitrophenylhydrazones on silica. The less strongly adsorbed hydrazone, m. p. 101°, gave no depression with that of 4 : 4-dimethylpentan-2-one. The other was acetone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126°.

The finely powdered glycol (348 g.) was added to concentrated sulphuric acid (3700 g.) at −10° to −15°, efficiently stirred. After being kept overnight, the solution was poured on ice (1·5 kg.), and the volatile products were removed by steam-distillation. The oil thus obtained was taken up in ether and fractionated after washing and drying. The main fraction, 3 : 3 : 5 : 5-*tetramethylhexan*-2-*one* (220 g.), n_D^{20} 1·4324, was collected at 74—77°/18 mm. The lower-boiling fractions were distilled again to give approximately pure 2 : 2 : 5 : 5-tetramethylhexan-3-one, b. p. 160—161°, n_D^{20} 1·4200 (15 g.). Unsaturated material was condensed in the cold traps of the earlier distillations but no pure substance was isolated.

3 : 3 : 5 : 5-Tetramethylhexan-2-one, b. p. 70—71°/13 mm., n_D^{20} 1·4326, d_{20}^{20} 0·8441 (Found : C, 76·8; H, 13·1. $C_{10}H_{20}O$ requires C, 76·85; H, 12·9%) is a mobile liquid of faint camphoraceous odour and gives a 2 : 4-*dinitrophenylhydrazone*, orange-yellow, m. p. 109·5—110° (Found : C, 57·3; H, 7·1; N, 16·6. $C_{16}H_{24}O_4N_4$ requires C, 57·1; H, 7·2; N, 16·7%), and a *semicarbazone*, m. p. 188° (Found : C, 62·25; H, 11·0; N, 19·5. $C_{11}H_{23}ON_3$ requires C, 61·9; H, 10·9; N, 19·7%). Reduction of the ketone in ether with lithium aluminium hydride gives 3 : 3 : 5 : 5-*tetramethylhexan*-2-*ol*, b. p. 87—87·5/27 mm., n_D^{20} 1·4458 (Found : C, 76·0; H, 13·9. $C_{10}H_{22}O$ requires C, 75·85; H, 14·0%) [3 : 5-*dinitrobenzoate*, m. p. 83·5—84° (Found : C, 58·0; H, 6·6; N, 8·4. $C_{17}H_{24}O_6N_2$ requires C, 57·9; H, 6·9; N, 8·0%)]. The ketone (3 g.) was added slowly to nitric acid (*d* 1·42; 25 c.c.) diluted with an equal volume of water, and then heated under reflux for 8 hr. The mixture was diluted with water and extracted with benzene. Unchanged ketone and 2 : 4 : 4-trimethylpentane-2-carboxylic acid, b. p. 119—121°/13 mm., m. p. 43—45°, were obtained. The m. p. of the acid was unchanged on admixture with an authentic specimen (Whitmore, Wheeler, and Surmatis, *J. Amer. Chem. Soc.*, 1941, **63**, 3237); the p-*toluidide* had m. p. 116° (Found : C, 77·6; H, 10·5; N, 5·9. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·2; N, 5·7%).

2 : 2 : 5 : 5-Tetramethylhexan-3-one, b. p. 160—161°, gives no ketonic derivatives. Whitmore and Heyd (*J. Amer. Chem. Soc.*, 1938, **60**, 2030) claim that a 2 : 4-dinitrophenylhydrazone, m. p. 123·5—124·5°, is formed with considerable difficulty. We are unable to confirm this. The ketone is best identified by reduction to 2 : 2 : 5 : 5-tetramethylhexan-3-ol, m. p. and mixed m. p. 50—51° (Whitmore and Heyd, *loc. cit.*, give m. p. 49·4°) [3 : 5-*dinitrobenzoate*, m. p. 146° (Found : C, 57·8; H, 6·8; N, 8·0. $C_{17}H_{24}O_6N_2$ requires C, 57·9; H, 6·9; N, 8·0%)].

Preparation and Rearrangement of 2 : 4-*Dimethyl*-3-iso*propylpentane*-2 : 3-*diol*.—Methyl-lithium [from lithium (21 g.), methyl bromide, and ether (1300 c.c.)] with 3-hydroxy-4-methyl-3-*iso*propylpentan-2-one (95 g.) gave crystalline 2 : 4-*dimethyl*-3-iso*propylpentane*-2 : 3-*diol* (52·5 g.) with lower-boiling fractions of unchanged ketol. In subsequent preparations the yield was raised to 80% by distilling off the ether, replacing it with dry benzene, and refluxing for 8 hr. The pure glycol, m. p. 68° (from light petroleum, b. p. 40—60°), b. p. 119°/18 mm. (Found : C, 68·9; H, 12·55. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·75%), was oxidised by periodic acid in aqueous methanol to acetone and di*iso*propyl ketone, identified as 2 : 4-dinitrophenylhydrazones.

The glycol (100 g.) was added slowly to concentrated sulphuric acid (1000 g.) at −10° to 0°, with stirring. The mixture was kept at −5° for 3 hr., then poured on crushed ice (2 kg.),

and steam-distilled after further dilution. The volatile product was removed with ether, washed with aqueous sodium carbonate, dried, and fractionated into two main fractions: (*a*) b. p. 79°/22 mm., n_D^{20} 1·4284 (52 g.), (*b*) b. p. 84—88°/22 mm., n_D^{20} 1·4398—1·4416 (14·3 g.); residue, 4·6 g. The most volatile fractions were collected in a cold trap, and amounted to 4·8 g., of which 1·7 g. had b. p. 60—65°, n_D^{20} 1·3604, and consisted essentially of acetone. No other compound could be identified with certainty; some olefinic compounds were present; no di*iso*propyl ketone was found.

Refractionation of (*a*) gave pure **2 : 4 : 4 : 5-*tetramethylhexan*-3-*one***, b. p. 79°/22 mm., n_D^{20} 1·4275, a colourless liquid of camphoraceous odour (Found: C, 77·3; H, 13·0. $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%). No carbonylic derivatives could be prepared from it, but reduction with lithium aluminium hydride gave **2 : 4 : 4 : 5-*tetramethylhexan*-3-*ol***, b. p. 85—86°/16 mm., n_D^{20} 1·4492 (Found: C, 76·1; H, 14·0. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%) [**3 : 5-*dinitrobenzoate***, m. p. 76° (Found: C, 58·0; H, 7·15; N, 8·0. $C_{17}H_{24}O_6N_2$ requires C, 57·9; H, 6·9; N, 8·0%)]. With boiling nitric acid (*d* 1·42) diluted with half its volume of water the ketone gave ααβ-trimethylbutyric acid, characterised as the amide, m. p. 129° (Found: C, 65·3; H, 11·4; N, 10·2. Calc. for $C_7H_{15}ON$: C, 65·1; H, 11·6; N, 10·8%), and p-*toluidide*, m. p. 91—92° (Found: C, 77·0; H, 10·0; H, 6·3. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·7; N, 6·4%).

Fraction (*b*) gave pure **3 : 4-*dimethyl*-3-iso*propylpentan*-2-*one*** on further distillation, as a pale yellow liquid, b. p. 87—88°/22 mm., n_D^{20} 1·4415 (Found: C, 77·1; H, 12·8. $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%). Neither semicarbazone nor 2 : 4-dinitrophenylhydrazone could be prepared. The nitroprusside test was positive. Reduction with lithium aluminium hydride afforded **3 : 4-*dimethyl*-3-iso*propylpentan*-2-*ol***, b. p. 100°/16 mm., n_D^{20} 1·4619 (Found: C 76·1; H, 13·9. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%) [**3 : 5-*dinitrobenzoate***, m. p. 80—81° (Found: C, 58·0; H, 7·3; N, 7·7. $C_{17}H_{24}O_6N_2$ requires C, 57·9; H, 6·9; N, 8·0%)]. With hot nitric acid (1 : 1) the ketone gave αβ-dimethyl-α-*iso*propylbutyric acid [p-*toluidide*, m. p. 116° (Found: C, 78·1; H, 10·2; N, 5·5. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·2; N, 5·7%)].

2 : 3 : 4 : 4 : 6 : 6-*Hexamethylheptane*-2 : 3-*diol and its Fission by Sulphuric Acid.*—A solution of 3-hydroxy-3 : 4 : 4 : 6 : 6-pentamethylheptan-2-one (260 g.) in dry ether (200 c.c.) was added dropwise to methyl-lithium (from 45·5 g. of lithium and 3 l. of ether), so that gentle reflux was maintained. The mixture was then heated under reflux for 2 hr., the bulk of the solvent (2200 c.c.) was distilled off, and the residue heated under reflux for 10 hr. The product was worked up as usual to give **2 : 3 : 4 : 4 : 6 : 6-*hexamethylheptane*-2 : 3-*diol***, b. p. 104—106°/1·8 mm., n_D^{20} 1·4672, a very viscous liquid (Found: C, 72·13; H, 12·95. $C_{13}H_{28}O_2$ requires C, 74·15; H, 13·0%). It is oxidised by periodic acid in aqueous methanol to acetone and **3 : 3 : 5 : 5-**tetramethylhexan-2-one, identified as 2 : 4-dinitrophenylhydrazones, m. p.s and mixed m. p.s 125° and 110° respectively.

The diol (230 g.) was added slowly to concentrated sulphuric acid (1·5 l.) at −10° to 0°, stirring and cooling being continued for 2 hr. after the addition. The solution was then poured on crushed ice and steam-distilled after further dilution. The volatile products were collected with ether, washed, dried, and fractionally distilled. In the cold trap, distillate (A) (55·6 g.) was collected; the remainder (B) (92 g.) distilled between 40°/8 mm. and 90°/2 mm. There was a considerable tarry residue. The material (A) distilled between 90° and 95° (47·3 g.) and the fraction of b. p. 94—95° was substantially pure methyl *iso*propyl ketone, n_D^{20} 1·3889 (semicarbazone, m. p. and mixed m. p. 112—113°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 117°). There was a small amount of unsaturated material in the fraction of b. p. 95—100°. The distillate (B) showed a steady rise in b. p. and refractive index without much evidence of separation. All the fractions were unsaturated and the following analyses show that they consisted substantially of unsaturated hydrocarbons:

Fraction	B. p./mm.	n_D^{20}	C (%)	H (%)	*M*	Fraction	B. p./mm.	n_D^{20}	C (%)	H (%)	*M*
3	50—58°/8	1·4303	84·0	14·25	170	9	60—66°/2	1·4528	85·5	13·5	185
5	50—54°/4	1·4450	84·4	13·7	166	11	72—76°/2	1·4589	85·7	13·3	189
7	60—68°/4	1·4483	85·1	13·6	173	13	82—90°/2	1·4660	85·5	13·3	203

UNIVERSITY OF LONDON, QUEEN MARY COLLEGE,
MILE END ROAD, LONDON, E.1.

[*Received, February 27th*, 1954.]

Synthesis of 10-*Hydroxy*-4 : 5 : 6-*trimethoxyaporphine.*

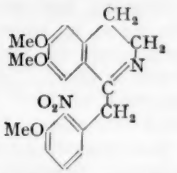
By T. R. Govindachari and K. Nagarajan.

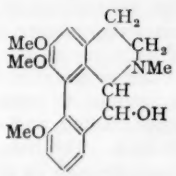
[Reprint Order No. 5174.]

The synthesis of 10-hydroxy-4 : 5 : 6-trimethoxyaporphine is reported.

The principal alkaloid from *Artabotrys suaveolens*, Bl., was originally considered to be 10-hydroxy-4 : 5 : 6-trimethoxyaporphine (II) (Barger and Sargent, *J.*, 1939, 991). The synthesis of a compound having this structure was effected by the following procedure. Oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline (I) (Govindachari and Pai, *J. Org. Chem.*, 1953, **18**, 1352) with potassium dichromate yielded 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline, which was then reduced to 1-(α-hydroxy-3-methoxy-2-nitrobenzyl)-6 : 7-dimethoxy*iso*quinoline by aluminium *iso*propoxide in toluene or by sodium borohydride in cold methanol. The methiodide of the

(I)





(II)

last base was reduced in methanol in the presence of Adams catalyst to 1-(2-amino-α-hydroxy-3-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl-*iso*quinoline. When the synthesis had been brought to this stage, a publication by Schlittler and Huber (*Helv. Chim. Acta*, 1952, **35**, 111) appeared proving that the so-called " artabotrine " was identical with *iso*corydine. Nevertheless, the last step in the synthesis was completed in view of Schlittler and Lindenmann's finding (*ibid.*, 1949, **32**, 1880) that oxoaporphines were formed in much better yield than the corresponding aporphines in the Pschorr reaction and it was of interest to know whether this would be true of 10-hydroxy-aporphines also. However, 10-hydroxy-4 : 5 : 6-trimethoxyaporphine (II) was formed in less than 1% yield, whereas 4 : 5 : 6-trimethoxyaporphine itself has been obtained (Govindachari and Pai, *loc. cit.*) in about 10% yield.

Experimental

Ultra-violet absorption spectra were measured for absolute ethanol solutions with a Beckman Model DUV Spectrophotometer. Some analyses are by Mr. S. Selvavinayagam.

6 : 7-*Dimethoxy*-1-(3-*methoxy*-2-*nitrobenzoyl*)iso*quinoline*.—To a solution of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline (Govindachari and Pai, *loc. cit.*) (5 g.) in 70% acetic acid (40 ml.) was added finely powdered potassium dichromate (10 g.), and the mixture refluxed for 2 hr. The mixture was then cooled and filtered. The residue was washed with dilute acetic acid and then with water (filtrate A). Crystallisation of the residue from alcohol yielded the benzoyl*iso*quinoline as pale yellow needles (3·03 g.), m. p. 212° (decomp.), $\lambda_{max.}$ 232 (log ε 4·70) and 350 mμ (log ε 3·93) (Found : C, 61·5; H, 4·4; N, 7·5. $C_{19}H_{16}O_6N_2$ requires C, 61·9; H, 4·3; N, 7·6%).

The filtrate A was diluted with a large volume of water and extracted with chloroform. The residue obtained from the dried chloroform extract was crystallised from water and then from alcohol, yielding a *substance* as bright yellow needles (0·10 g.), m. p. 245—247°, which was not further characterised (Found : C, 57·0; H, 4·1; N, 6·7. $C_{19}H_{16}O_8N_2$ requires C, 57·0; H, 4·0; N, 7·0%).

1-(α-*Hydroxy*-3-*methoxy*-2-*nitrobenzyl*)-6 : 7-*dimethoxy*iso*quinoline*.—(a) *Reduction by aluminium* iso*propoxide*. A solution of the foregoing 1-benzoyl*iso*quinoline (1 g.) in dry thiophen-free toluene (20 ml.) was refluxed with aluminium *iso*propoxide (2·3 g.) for 4 hr. The mixture was distilled with addition of dry *iso*propyl alcohol (75 ml.) in three equal portions, till the distillate was free from acetone and then cooled. The aluminium complex was decomposed by 4N-sulphuric

acid (25 ml.), and the toluene layer separated. The acid layer was rendered strongly alkaline with sodium hydroxide solution and extracted with benzene. The dried benzene extract, after removal of solvent, yielded the *alcohol* (0·86 g.) which after crystallisation from alcohol melted at 180° (decomp.), $\lambda_{max.}$ 242 (log ε 4·78), 315 (log ε 3·73), and 325 mμ (log ε 3·80) (Found : C, 61·6; H, 4·9; N, 7·3. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9; N, 7·6%).

The *acetate*, prepared by acetic anhydride in pyridine, crystallised from alcohol as colourless needles, m. p. 197° (Found : C, 61·1; H, 4·8; N, 7·2. $C_{21}H_{20}O_7N_2$ requires C, 61·1; H, 4·9; N, 6·8%). The *methiodide*, prepared at 100°, crystallised from methanol as pale yellow needles, m. p. 207° (decomp.) (Found : C, 46·9; H, 4·5; N, 5·6; I, 24·6. $C_{20}H_{21}O_6N_2I$ requires C, 46·9; H, 4·1; N, 5·5; I, 24·8%).

(b) *Reduction by sodium borohydride*. The 1-benzoyl*iso*quinoline (5 g.) was suspended in acetone-free methyl alcohol (50 ml.), and sodium borohydride (2·5 g.) was added. The mixture was shaken frequently and the temperature was kept below 30°. The benzoyl*iso*quinoline gradually disappeared and a fluffy material separated. Water (100 ml.) was added and the precipitate was collected, washed free from alkali, and dried *in vacuo*. The hydroxy-base so obtained (4·75 g.) melted at 180° (decomp.).

1-(2-*Amino*-α-*hydroxy*-3-*methoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinoline.—A suspension of the methiodide of the foregoing hydroxy-base (2·5 g.) in methyl alcohol (150 ml.) was shaken with hydrogen at 60 lb. per sq. in. after addition of Adams catalyst (0·18 g.), till absorption of hydrogen ceased. The solution was filtered from the catalyst and the filtrate rendered acidic and evaporated to dryness *in vacuo*. The residue was dissolved in water and extracted with benzene to remove non-basic matter. The aqueous solution was then made alkaline after good cooling, and extracted with ether. Purification was effected by one more passage through acid. The base was then converted into the dihydrochloride by passing dry hydrogen chloride through its ether solution. Crystallisation of the crude *dihydrochloride* (1·54 g.) from absolute alcohol yielded the pure salt, m. p. 208° (decomp.) (Found : C, 55·3; H, 6·7; N, 6·6; Cl, 16·5. $C_{20}H_{28}O_4N_2Cl_2$ requires C, 55·7; H, 6·5; N, 6·5; Cl, 16·5%).

10-*Hydroxy*-4 : 5 : 6-*trimethoxyaporphine*.—A solution of the foregoing dihydrochloride (2·0 g.) in methyl alcohol (15 ml.) and 2N-sulphuric acid (20 ml.) was cooled to 0° and treated with sodium nitrite (0·31 g.) in water (20 ml.) at <3°. After 1 hr. at 0°, the slight excess of sodium nitrite was decomposed by sulphamic acid. Freshly prepared copper powder (2 g.) was added to the solution which was allowed to come to room temperature and then heated on water-bath till evolution of nitrogen ceased. Zinc dust (1 g.) and 10N-hydrochloric acid (2 ml.) were then added and the mixture was heated on a water-bath for a further hour. The colourless solution was filtered from the zinc residue. The filtrate was cooled, rendered alkaline, and extracted with ether. The ether extract was stripped of basic material by shaking it with N-hydrochloric acid. The acid extract was made almost neutral by addition of sodium hydrogen carbonate and then saturated with potassium iodide. A brownish gum separated, from which the clear supernatant liquid was decanted.

The gum was extracted repeatedly with boiling water. The aqueous extract was decolorised by norite, cooled, rendered alkaline, and extracted with ether. The dried ether extract yielded on removal of solvent an oil (0·2 g.) which was repeatedly extracted with boiling light petroleum (b. p. 40—60°). The combined extracts were concentrated to 100 ml. The amorphous material which separated on cooling was removed by filtration. Further concentration to 10 ml. yielded a crystalline solid. Recrystallisation from benzene–light petroleum gave 10-*hydroxy*-4 : 5 : 6-*trimethoxyaporphine* (0·01 g.), m. p. 180°, $\lambda_{max.}$ 273 (log ε 4·10) and 300 mμ (log ε 4·01) (Found : C, 70·9; H, 7·2. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·8%).

The supernatant liquid decanted from the gummy hydriodide was rendered alkaline and extracted with ether. The dried ether extract on removal of solvent yielded 0·33 g. of a waxy *substance*, which gave colourless needles (0·18 g.), m. p. 138—139°, after crystallisation from alcohol (Found : C, 63·9; H, 7·3; N, 7·7. $C_{20}H_{26}O_5N_2$ requires C, 64·2; H, 7·0; N, 7·5%). This product could not be further characterised.

We thank the Government of India for the award of a scholarship to one of us (K. N.).

PRESIDENCY COLLEGE, MADRAS. [*Received, March 2nd*, 1954.]

The Reaction of Chloroacetone with Aryl Grignard Reagents.

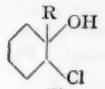
By R. L. Huang.

[Reprint Order No. 5175.]

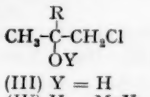
The products obtained by the reaction named in the title vary according to the nature of the aryl group.

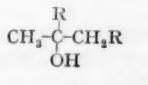
The reaction of 2-chloro*cyclo*hexanone with aryl Grignard reagents (Huang, *J. Org. Chem.*, in the press) proceeds by normal addition of the reagent to the carbonyl group; the resulting complex can then give rise to either the chlorohydrin (I) or the rearranged ketone (II) according to whether R is of low or high electropositivity, respectively. It seemed of interest to study the same reaction with chloroacetone, the simplest member of the chloroketones and free from steric complications.

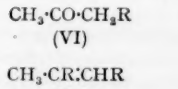
It is known that chloroacetone on reaction with phenylmagnesium bromide and subsequent hydrolysis furnishes the normal addition product, namely, the chlorohydrin (III), but that heating of the magnesium complex before hydrolysis results in a rearranged product, phenylacetone (Tiffeneau, *Ann. Chim.*, 1907, **10**, 367). The action on chloroacetone of a two-fold excess of Grignard reagent containing the typical aromatic groups has now given the following results.


(I)

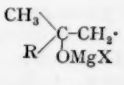
(II)


(III) Y = H
(IV) Y = MgX


(V)


(VI)

(VII)


(VIII)

(i) Strongly electron-releasing groups (*p*-ethoxyphenyl and *p*-methoxyphenyl) yield exclusively the substituted stilbenes (VII), undoubtedly derived from the alcohols (V) by dehydration. When, however, only a 0·5 mole excess of the reagent was used, the ketone (VI; R = *p*-MeO·C_6H_4) also was isolated in small yields. (ii) Weakly electron-releasing groups (*m*- and *p*-chlorophenyl) furnished the chlorohydrins (III) only. (iii) An *ortho*-substituted aryl group (*o*-methoxyphenyl) also yielded the chlorohydrin (III).

As with 2-chloro*cyclo*hexanone, therefore, the ultimate product of the reaction depends on the nature of the aryl group, highly electropositive groups leading to rearranged products. In the former case, however, the *cyclo*hexanone (II) was obtained, and it is not clear whether rearrangement had taken place before or after hydrolysis of the magnesium complex. With chloroacetone it appears probable that this complex had undergone rearrangement to the ketone (VI), which then reacted with more Grignard reagent to give the alcohol (V). This rearrangement might proceed *via* a free-radical intermediate such as (VIII), which could be generated from the complex (IV) by a one-electron transfer to the chlorine atom either from unchanged magnesium in the Grignard reagent, or from a component of the equilibrium $2RMgX \rightleftharpoons R_2Mg + MgX_2$. The fact that a filtered Grignard solution did not alter the course of the reaction, however, excludes the former possibility.

Experimental

Microanalyses were carried out in the microanalytical laboratory, Organic Chemistry Department, Imperial College of Science and Technology (Mr. F. H. Oliver), London.

Reaction of Chloroacetone with p-*Ethoxyphenylmagnesium Bromide.*—Chloroacetone (9·2 g., 0·10 mole) in ether (50 c.c.) was added during 0·5 hr. with stirring to the Grignard reagent prepared from *p*-bromophenetole (44 g., 0·20 mole) and magnesium (5·3 g., 0·22 mole) in ether (*ca.* 100 c.c.) with external cooling (ice and water). Stirring was then continued for 1 hr. at room temperature (28°). Next day the mixture was decomposed with concentrated aqueous ammonium chloride, and the product taken up in ether, and washed with aqueous ammonium chloride, then water; the solution was filtered from an ether-insoluble amorphous solid (*ca.* 2 g.) and dried (Na_2SO_4). The ether was evaporated, and after being heated on the steam-bath for 0·5 hr. and cooled the product solidified. It was treated with a little ethanol and filtered off,

giving 4 : 4′-*diethoxy-α-methylstilbene* (crude, 12 g.) which crystallised from ethanol in woolly needles, m. p. 108—109° (Found : C, 80·9; H, 8·1. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%).

Reaction with p-*Methoxyphenylmagnesium Bromide.*—(a) *With filtered Grignard reagent.* The product from chloroacetone (7·3 g., 0·08 mole) and *p*-methoxyphenylmagnesium bromide (0·18 mole, filtered under nitrogen pressure through glass wool) was worked up as before, yielding 4 : 4′-dimethoxy-α-methylstilbene (18 g.), m. p. 124° (Found : C, 80·0; H, 7·1. Calc. for $C_{17}H_{18}O_2$: C, 80·3; H, 7·1%). Dodds, Goldberg, Grunfeld, Lawson, Saffer, and Robinson report m. p. 123—124° (*Proc. Roy. Soc.*, 1944, *B*, **132**, 83).

(b) *With 0·5 mole excess of the Grignard reagent.* The product from chloroacetone (13·8 g.) gave in part 4 : 4′-dimethoxy-α-methylstilbene (8·5 g.) which separated as a solid and was filtered off. The filtrate was distilled, giving (i) a yellow liquid, b. p. 102—104°/0·5 mm. (1·6 g.), which was mainly *p*-methoxyphenylacetone, and (ii) a tarry residue (12 g.). Fraction (i) quickly darkened, but readily formed *p*-methoxyphenylacetone semicarbazone, m. p. 174—176° (from ethanol) (lit., m. p. 175), and a 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 104—105° (Found : C, 55·7; H, 4·5. $C_{16}H_{16}O_5N_4$ requires C, 55·7; H, 4·65%).

p-Chlorophenylmagnesium bromide (0·2 mole), on reacting with chloroacetone (9·2 g., 0·1 mole), gave, as the main product, 1-*chloro*-2-p-*chlorophenylpropan*-2-*ol* (12 g.), b. p. 100—102°/1 mm., n_D^{20} 1·5568. This appeared to be contaminated with traces of a ketone (probably VI) which could not be effectively removed by distillation. A portion (2·5 g.), treated with Girard reagent P (1 g.) in the usual manner, afforded a pure sample, b. p. 100°/1 mm., n_D^{20} 1·5554 (Found : C, 53·0; H, 5·0. $C_9H_{10}OCl_2$ requires C, 52·7; H, 4·9%). The ketonic material (<0·1 g.) extracted by the reagent gave small quantities of an orange-red 2 : 4-dinitrophenylhydrazone.

m-Chlorophenylmagnesium bromide (0·068 mole) and chloroacetone (3·1 g., 0·034 mole) gave 1-*chloro*-2-m-*chlorophenylpropan*-2-*ol* (4·2 g.), b. p. 103—105°/1 mm., n_D^{21} 1·5558 (Found : Cl, 34·2. $C_9H_{10}OCl_2$ requires Cl, 34·6%).

o-Methoxyphenylmagnesium bromide (0·20 mole) and chloroacetone (11 g., 0·12 mole) yielded 1-*chloro*-2-o-*methoxyphenylpropan*-2-*ol* (10·2 g.), b. p. 107—110°/0·5 mm., n_D^{23} 1·5442 (Found : C, 60·1; H, 6·5; Cl, 17·8. $C_{10}H_{13}O_2Cl$ requires C, 59·9; H, 6·5; Cl, 17·7%).

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, March 2nd*, 1954.]

4-*Aminosalicylaldehyde.*

By A. A. GOLDBERG and H. A. WALKER.

[Reprint Order No. 5195.]

Bromination of 2-acetoxy-4-nitrotoluene gave a difficultly separable mixture of 2-acetoxy-4-nitrobenzyl bromide and 2-acetoxy-4-nitrobenzylidene dibromide. Treatment of the mixture with pyridine, however, afforded 2-hydroxy-4-nitrobenzylpyridinium bromide in good yield which was converted by the Kröhnke reaction into 4-nitrosalicylaldehyde. 4-Amino- and 4-acylamino-salicylaldehyde thiosemicarbazones were made from this in order to assess their antimycobacterial activites.

4-AMINO- AND 4-ACYLAMINO-SALICYLALDEHYDE THIOSEMICARBAZONES were required because they bear structural resemblance to 4-acetamidobenzaldehyde thiosemicarbazone and to 4-aminosalicylic acid, both of which compounds possess high activity against *Mycobacterium tuberculosis*. [Since the work described below was completed, Seymour, Drain, and Suddaby (B.P. 684,616) have described the preparation of 4-acetamidosalicylaldehyde thiosemicarbazone by a different method which does not, however, lend itself to large-scale application.]

The necessary intermediate, 4-nitrosalicylaldehyde, was obtained by Segusser and Calvin (*J. Amer. Chem. Soc.*, 1942, **64**, 825) in unspecified yield by bromination of 2-acetoxy-4-nitrotoluene and hydrolysis of the 2-acetoxy-4-nitrobenzylidene dibromide produced. Repetition of this procedure showed that the low yield (*ca.* 10%; cf. Libermann, Desnoes, and Hengl, *Compt. rend.*, 1951, **232**, 2027) was due to reluctance

of 2-acetoxy-4-nitrotoluene to undergo dibromination and difficulty of separation of mono- and di-bromination products. Examination of the reaction indicated that bromination of the substituted toluene with 2 mols. of bromine in boiling tetrachloroethane (see Table) produced the optimum amount of 2-acetoxy-4-nitrobenzyl bromide. Although this could not be isolated as such without great loss, treatment of the mixture with moist pyridine gave pure 2-hydroxy-4-nitrobenzylpyridinium bromide in acceptable yield; this was suitable for conversion into the required aldehyde by Kröhnke's reaction (*Ber.*, 1936, **69**, 2006; 1938, **71**, 2583; 1939, **72**, 440). Treatment of the quaternary salt with *NN*-dimethyl-*p*-nitrosoaniline and sodium hydroxide yielded the nitrone, 2-hydroxy-4-nitrobenzaldoxime *N*-*p*-dimethylaminophenyl ether, which without isolation was rapidly converted by dilute acid into 4-nitrosalicylaldehyde. Reduction of the thiosemicarbazone with hydrogen or ammonium sulphide yielded 4-aminosalicylaldehyde thiosemicarbazone; this, on treatment with acyl anhydrides or halides, gave the desired 4-acylaminosalicylaldehyde thiosemicarbazones.

Chemotherapeutic Properties.—Mice (20 g.), in groups of ten, each mouse infected with *M. tuberculosis* (Ravenel strain; 1 million organisms per mouse) and each fed with 75 or 150 mg./kg. doses daily of (i) 4-amino- (LD50 2·6 g./kg.), (ii) 4-acetamido- (LD50 3·0 g./kg.), (iii) 4-benzamido- (LD50 3·5 g./kg.), and (iv) 4-hexanamido-salicylaldehyde thiosemicarbazone (LD50 3·1 g./kg.) failed to survive for 25 days. The untreated controls died in 14—20 days; infected mice given 75 mg./kg. of 4-acetamidobenzaldehyde thiosemicarbazone (LD50 0·8 g./kg.) or 1250 mg./kg. of 4-aminosalicylic acid (LD50 4·0 g./kg.) daily survived for 35 days.

Experimental

2-Acetoxy-4-nitrobenzyl Bromide.—2-Methyl-5-nitrophenol (100 g.) was slowly added to stirred acetic anhydride (100 c.c.), and the mixture heated on the water-bath for 1 hr., cooled, and then poured into ice-water (600 c.c.). After ½ hour's stirring the crude 2-acetoxy-4-nitrotoluene (116 g.) was collected, washed, and dried at 40°/10 mm.; this had m. p. 70—74° and was pure enough for use. Dry bromine (23 g., 0·145 mol.) was added during 4 hr. to a refluxing solution of 2-acetoxy-4-nitrotoluene (28 g., 0·14 mol.) in dry carbon tetrachloride (400 c.c.), and the solution then refluxed for a further 24 hr. Solvent was removed and the residue crystallised from dried *n*-butanol; *2-acetoxy-4-nitrobenzyl bromide* (10 g., 26%) separated in plates, m. p. 79° (Found: Br, 29·1. $C_9H_8O_4NBr$ requires Br, 29·2%). Attempts to convert this into 4-nitrosalicylaldehyde by the Sommelet reaction were not very successful. Thus, hexamine (7 g.) was added rapidly to a refluxing solution of the foregoing bromide (10 g.) in acetic acid (25 c.c.). Refluxing was continued for a further ¼ hr. and the clear solution distilled in steam; 4-nitrosalicylaldehyde (0·5 g., 7%) came over in pale yellow plates, m. p. 132°. The method was abandoned in favour of the following.

2-Hydroxy-4-nitrobenzylpyridinium Bromide.—A solution of dry bromine (128 g., 0·8 mol.) in redistilled tetrachloroethane (40 c.c.) was added during 4 hr. to a refluxing solution of 2-acetoxy-4-nitrotoluene (80 g., 0·4 mol.) and iodine (0·2 g.) in tetrachloroethane (160 c.c.) in a quartz flask irradiated by a 500-watt ultra-violet lamp emitting in the 3000—3600 Å range. Refluxing was continued for a further 2 hr. by which time evolution of hydrogen bromide had ceased; solvent was pumped off and the residual oil (A) dissolved in 95% alcohol (160 c.c.). Pyridine (50 c.c.) was added with shaking, whereupon the mixture developed sufficient heat to effect refluxing of the alcohol and simultaneous separation of *2-hydroxy-4-nitrobenzylpyridinium bromide*. After storage overnight at room temperature, the crystalline precipitate (88 g., 71%; m. p. 264—266°) was collected, washed with a small amount of 90% alcohol, and dried; a sample separated from dilute alcohol in needles, m. p. 268° (Found: N, 9·2; Br, 25·9. $C_{12}H_{11}O_3N_2Br$ requires N, 9·0; Br, 25·7%). Use of a Pyrex flask caused a slight diminution in yield; in reactions carried out without ultra-violet illumination the yield was 63%. In one experiment the dark oil (A) resulting from the foregoing bromination was diluted with tetrachloroethane (400 c.c.), and this solution mixed with dry pyridine (100 c.c.) and heated on the water-bath for 1 hr.; on cooling, *2-acetoxy-4-nitrobenzylpyridinium bromide*, m. p. 230°, separated (Found: N, 8·1; Br, 22·9. $C_{14}H_{13}O_4N_2Br$ requires N, 7·9; Br, 22·6%). The same compound was obtained by refluxing 2-hydroxy-4-nitrobenzylpyridinium bromide with four times its weight of acetic anhydride for a short time.

The action of bromine under varying conditions upon 2-acetoxy-4-nitrotoluene is shown in

the annexed Table. The last column gives the amount of 2-acetoxy-4-nitrobenzyl bromide formed, as assessed by the yield of 2-hydroxy-4-nitrobenzylpyridinium bromide obtained by treatment with moist pyridine.

Bromination of 2-*acetoxy*-4-*nitrotoluene with bromine.*

Bromine (mol.)	Addition time (hr.)	Reflux time after addition (hr.)	Solvent	Yield (%)
1	5	12	CCl_4	11
4	9	12	,,	52
1	2·5	20	$C_2H_3Cl_4$	23
1·5	0·5	4	,,	39
2	3·5	5	,,	71
2	4·0	6	,,	70
3	2·5	4	,,	52

Bromination of 2-*Acetoxy*-4-*nitrotoluene with* N-*Bromosuccinimide and* N-*Bromophthalimide*.—(i) A mixture of 2-acetoxy-4-nitrotoluene (9·8 g., 0·05 mol.), *N*-bromosuccinimide (10 g., 0·056 mol.), benzoyl peroxide (0·2 g.), and tetrachloroethane (15 c.c.) was gently heated until a vigorous reaction set in; when this had subsided the mixture was refluxed for ½ hr. and kept overnight. The succinimide was filtered off, the solvent pumped off, and the residual oil refluxed for 1 hr. with 95% alcohol (20 c.c.) and pyridine (8 c.c.); 2-hydroxy-4-nitrobenzylpyridinium bromide (2·2 g., 15%) was obtained.

(ii) 2-Acetoxy-4-nitrotoluene (19·8 g., 0·1 mol.), *N*-bromophthalimide (24 g., 0·105 mol.), and tetrachloroethane (60 c.c.) were heated on the water-bath for 4 hr. and then the mixture refluxed for 4 hr. In the morning the precipitated phthalimide (9·9 g.) was removed and the filtrate treated as above described; the yield was 3 g. (24%).

4-*Nitrosalicylaldehyde*.—A suspension of 2-hydroxy-4-nitrobenzylpyridinium bromide (62·4 g., 0·2 mol.) and freshly prepared *NN*-dimethyl-*p*-nitrosoaniline (30 g., 0·2 mol.) in 96% alcohol (320 c.c.) was rapidly stirred at room temperature. N-Sodium hydroxide (400 c.c., 0·4 mol.) was added, stirring continued for 2 hr., and the dark red mixture set aside overnight (B); in the morning 5N-hydrochloric acid (800 c.c., 4 mol.) was added and the mixture stirred at room temperature for ½ hr. The brick-red precipitate of 4-nitrosalicylaldehyde (28 g., m. p. 130°) was collected, washed with water, and dissolved in boiling alcohol (150 c.c.), water (25 c.c.), and acetic acid (2 c.c.), and the filtered (charcoal) solution was diluted with boiling water (350 c.c.); 4-nitrosalicylaldehyde (20 g.) separated as glittering puce plates, m. p. 134° (Found: N, 8·6. Calc. for $C_7H_5O_4N$: N, 8·4%). The compound is soluble in a large volume of water; it is volatile in steam, separating in the distillate as long yellow needles of the same m. p.

A solution of the foregoing aldehyde (28 g.) in boiling alcohol (400 c.c.) was added slowly to a stirred solution of thiosemicarbazide (40 g.) in water (1200 c.c.) at 90°. After a further ½ hour's stirring and storage overnight, the yellow precipitate of 4-*nitrosalicylaldehyde thiosemicarbazone* (35 g.), m. p. 260°, was collected (Found: N, 23·4; S, 13·2. $C_8H_8O_3N_4S$ requires N, 23·3; S, 13·3%).

The following derivatives of 4-nitrosalicylaldehyde were prepared and crystallised from the solvent stated in parentheses: *Oxime* (alcohol), long yellow needles, m. p. 192° (Found: N, 15·4. $C_7H_6O_4N_2$ requires N, 15·4%); *hydrazone* (alcohol), orange plates, m. p. 176° (Found: N, 23·0. $C_7H_7O_3N_3$ requires N, 23·2%); 2:4-*dinitrophenylhydrazone* (dilute pyridine), orange-red clusters of needles, m. p. >310° (Found: N, 20·2. $C_{13}H_9O_7N_5$ requires N, 20·2%); p-*thiocyanatophenylhydrazone* (aqueous pyridine), puce needles, m. p. 226° (decomp.) (Found: N, 17·6; S, 10·2. $C_{14}H_{10}O_3N_4S$ requires N, 17·8; S, 10·2%); and 2-*hydroxyethylhydrazone* (aqueous alcohol), needles, m. p. 112° (Found: N, 18·6. $C_9H_{11}O_4N_3$ requires N, 18·7%).

2-*Hydroxy*-4-*nitrobenzaldoxime* N-p-*Dimethylaminophenyl Ether*.—When the foregoing red liquor (B) was filtered, this *nitrone* (64 g.) was obtained; it crystallised from ethyl acetate in glistening red plates, m. p. 254° (Found: N, 14·1. $C_{15}H_{15}O_4N_3$ requires N, 13·95%). Stirring this with 2·5N-hydrochloric acid (800 c.c.) at room temperature for ½ hr. gave 4-nitrosalicylaldehyde (20 g.).

4-*Aminosalicylaldehyde Thiosemicarbazone*.—Hydrogen sulphide was passed into a stirred suspension of 4-nitrosalicylaldehyde thiosemicarbazone (16·5 g.) in 96% alcohol (85 c.c.) and aqueous ammonia (85 c.c.; *d* 0·880) for 4 hr. The resulting solution was refluxed for 1 hr. with stirring and then kept at room temperature overnight. The crystalline precipitate was collected and dissolved in 0·25N-sodium hydroxide (420 c.c.), and the filtered solution (charcoal) stirred and acidified with 25% acetic acid; the *product* (9·3 g.) separated as a yellow microcrystalline powder, m. p. 222—226° (decomp.) (Found: N, 26·5; S, 15·2. $C_8H_{10}ON_4S$ requires N, 26·7;

S, 15·3%). Acylating agents react with the 4-amino-group before attacking the thiosemicarbazide grouping.

4-*Acetamidosalicylaldehyde Thiosemicarbazone*.—Acetic anhydride (5 c.c.) was added to a solution of the foregoing amino-compound (10·5 g.) in pyridine (100 c.c.), and the mixture set aside overnight. Crystallisation of the precipitate (6·8 g.) from acetic acid gave the pure *acetyl* compound, m. p. 260—264° (decomp.) (Found: N, 22·3; S, 12·5. $C_{10}H_{12}O_2N_4S$ requires N, 22·2; S, 12·7%).

The following derivatives were prepared (with F. P. Jenkins): 4-*benzamidosalicylaldehyde thiosemicarbazone* (from aqueous methanol), orange microcrystalline powder, m. p. 180—186° (decomp.) (Found: N, 18·1; S, 10·0. $C_{15}H_{14}O_2N_4S$ requires N, 17·8; S, 10·2%); 4-*salicylamidosalicylaldehyde thiosemicarbazone* (from aqueous ethanol), orange needles, sinters at 200—210° (decomp.) (Found: N, 16·8; S, 9·5. $C_{15}H_{14}O_3N_4S$ requires N, 16·9; S, 9·7%); 4-n-*hexanamidosalicylaldehyde thiosemicarbazone* (from aqueous alcohol), orange powder, m. p. 260—266° (decomp.) (Found: N, 18·7; S, 10·5. $C_{14}H_{20}O_2N_4S$ requires N, 18·2; S, 10·4%).

Ward, Blenkinsop & Co., Ltd., Research Department,
Shepton Mallet, Somerset.

[*Received, March 10th*, 1954.]

Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part XIII. The Behaviour of Certain* N- *and* NN'- *Alkylated Benzidines towards Oxidising Agents.*

By R. Belcher, A. J. Nutten, and W. I. Stephen.

[Reprint Order No. 5101.]

N-Methyl-, *NN'*-dimethyl-, and *NN'*-tetramethyl-benzidine and the corresponding ethyl derivatives have been examined as colorimetric reagents for oxidising agents. These compounds are more sensitive towards oxidising agents than are the simple diamines; the products of their oxidation are exceptionally stable. Their applicability as redox indicators is also discussed.

Benzidine has been widely used for the colorimetric determination of various oxidising agents, but suffers from the disadvantage that its coloured oxidised form is very unstable and the colour fades rapidly. In an earlier paper of this series, Belcher and Nutten (*J.*, 1951, 546) examined the reactions of several nuclear-substituted benzidines with oxidising agents and showed these to be more satisfactory reagents than benzidine. Little work has, however, been reported on the analytical applications of the *N*- and *NN'*-substituted benzidines, although Hovorka (*Coll. Czech. Chem. Comm.*, 1948, **13**, 520) has described the uses in analytical chemistry of several *NN'*-dialdobenzidines, and of *NN'*-diacetyl-, *NN'*-dibenzoyl-, and *N*-monovanillylidene-benzidine. *NN'*-Diphenylbenzidine, the immediate oxidation product of diphenylamine, has found several applications in colorimetry and is used extensively as a redox indicator.

We have now examined several mono-, di-, and tetra-*N*-alkylbenzidines in order to assess their applicability as analytical reagents and particularly to study their behaviour towards oxidising agents. In connection with their studies on the mechanism of the oxidation of Alphazurine-G, Adams and Hammaker (*Analyt. Chem.*, 1951, **23**, 744) examined the indicator properties of *NN'*-tetramethylbenzidine and its 3-sulphonic acid. Their findings and ours are compared below.

Reactions with Oxidising Agents.—All the *N*- and *NN'*-alkylbenzidines used gave highly coloured products with many oxidising agents. In dilute acetic acid, the colours obtained were greenish-blue for the monoalkyl-, greenish-yellow for the dialkyl-, and bright yellow for the tetra-alkyl-benzidines. The colours of the ethyl derivatives were generally less intense. In mineral acid, all the amines gave bright yellow oxidation products.

* Part XII, *J.*, 1953, 1334.

The sensitivities of the amines towards oxidising agents in both acetic acid and mineral acid solution were determined. The results for selected oxidising agents are given in the Tables below, with those for benzidine included for comparison.

Ion sensitivities (μg. per ml.): acetic acid solution.

Benzidine	MnO_4^{1-}	$Cr_2O_7^{2-}$	VO_3^{1-}	Fe^{3+}	$S_2O_8^{2-}$	IO_4^{1-}	ClO^{1-}	$Fe(CN)_6^{3-}$	Ref. to preptn
(Unsubst.)	0·3	4	5	—	5	8	0·7	2	
N-Me	0·1	0·5	1	0·8	2	2	0·1	0·5	1
NN'-Me_2	0·05	0·25	0·25	0·4	0·5	0·7	0·1	0·4	2
NN'-Me_4	0·1	0·5	0·5	0·5	0·6	1	0·3	0·3	3
N-Et	0·1	0·8	1	1	2	2	0·2	0·5	4
NN'-Et_2...	0·1	1	0·8	0·8	25	5	0·2	0·4-	5
NN'-Et_4...	0·1	2	0·8	7	2	8	0·5	0·5	6

1, Rassow, *J. pr. Chem.*, 1911, **84**, 273. 2, Willstätter and Kalb, *Ber.*, 1904, **37**, 3773. 3, Ullmann and Dieterle, *ibid.*, p. 23. 4, Rassow, *loc. cit.*, p. 349. 5, Bamberger and Tichvinsky, *Ber.*, 1902, **35**, 4190. 6, Ullmann and Dieterle, *loc. cit.*, p. 33.

Ion sensitivities (μg. per ml.): hydrochloric acid solution.

Benzidine	$Cr_2O_7^{2-}$	VO_3^{1-}	IO_3^{1-}	BrO_3^{1-}	IO_4^{1-}	$S_2O_8^{2-}$	Cl_2
(Unsubst.)	5	5	1	—	20	20	1
N-Me	1	1·5	0·2	4	3	1	0·5
NN'-Me_2	0·4	0·4	0·1	5	1	0·4	0·25
NN'-Me_4	0·6	0·6	0·1	4	1	0·7	0·2
N-Et	0·5	0·5	0·25	5	2	0·5	0·5
NN'-Et_2	2	1·5	0·1	5	2	10	0·25
NN'-Et_4	2	2	—	—	—	2	0·5

All the *N*- and *NN'*-alkylbenzidines examined are more sensitive than benzidine towards oxidising agents. In acetic acid solution, the sensitivities of the *N*-methyl derivatives tend to be greater than those of the corresponding *N*-ethyl compounds. Moreover, the oxidation colours of all these amines are very stable. Of the amines described, two in particular, *NN'*-dimethyl- and *NN'*-tetramethyl-benzidine, should prove useful reagents for the detection and perhaps determination of oxidising agents. They are superior in every respect to the simple diamines which generally provide only transient colours with many oxidising agents. The secondary and tertiary amino-groups do not prevent the formation of the coloured product, but they do appear to inhibit the further oxidation of the molecule.

If this be so, the secondary and tertiary bases derived from numerous diamines of the benzidine series should be of much greater value as colorimetric reagents than the diamines themselves. In this investigation only the *N*- and *NN'*-alkylated benzidines have been studied; it would be interesting to examine several *N*- and *NN'*-alkylated 2 : 7-diaminophenylene oxides or 2 : 7-diaminofluorenes since both simple diamines give colour reactions which are much more sensitive than those given by benzidine but very transient.

Applications as Redox Indicators.—Adams and Hammaker (*loc. cit.*) have recommended *NN'*-tetramethylbenzidine and its 3-sulphonic acid as indicators for the titration of ferrous solutions with ceric sulphate. In the present work, none of the indicators proved to be of use in ferrous–ceric sulphate titrations, as the slow development of colour gave sluggish end-points with over-consumption of reagent. The oxidised form of *NN'*-tetramethylbenzidine was remarkably stable at high temperatures and this suggested its application as an indicator in oxalate–ceric sulphate titrations, but again the end-points were sluggish.

The applications of these alkylated benzidines appear to lie, not in titrations using ceric sulphate or potassium dichromate as oxidants (for which satisfactory indicators are generally available), but in replacement of benzidine; *e.g.*, *NN'*-dimethyl- or *NN'*-tetramethylbenzidine should be satisfactory in the titration of gold with quinol, silver with bromide or iodide, or vanadate with ferrous iron. Belcher and Nutten (*J.*, 1951, 547, 548) found that, in these titrations, nuclear-substituted benzidines gave considerably improved end-points.

Preparation of Amines.—Methods for the preparation of all these alkylated benzidines

are described in the literature and with one exception they proved satisfactory: *N*-ethylbenzidine could not be obtained by the method of Rassow (*loc. cit.*), who obtained only a negligible yield (*ca.* 1%); Gilman *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 922) prepared this compound by reaction of diethylbarium with azobenzene and rearrangement of the substituted hydrazobenzene with acid. Both these preparations were unsuitable for our purposes and an alternative synthesis was evolved. 4-Amino-4′-nitrodiphenyl, dissolved in acetone, was heated in a sealed tube with ethyl iodide, affording 4-ethylamino-4′-nitrodiphenyl; on reduction with zinc dust and hydrochloric acid, 4-amino-4′-ethylaminodiphenyl (*N*-ethylbenzidine) was obtained.

Experimental

(I) *Sensitivity Determinations.—Solutions required. Amine reagents.* 1% Solutions of each base in 5% acetic acid and in 1N-hydrochloric acid.

Procedure. (i) Acetic acid solution. One drop of amine reagent in acetic acid was added to 1 ml. of the neutral test solution contained in a micro-test tube and the colour formed was viewed against a white background. The procedure was repeated with more dilute solutions of the oxidising ions until a change of colour was just observed after 30 sec.

(ii) Hydrochloric acid solution. The above procedure was repeated but with the amine reagents in hydrochloric acid.

(II) *Applications as Redox Indicators.—Solutions required. Indicator solutions.* 1 g. of each base was dissolved in 100 ml. of 1N-sulphuric acid.

Ceric sulphate. 0·1N (*J.*, 1952, 1273).

Titration of ferrous iron. 0·1N-Ferrous ammonium sulphate solution (see *J.*, 1952, 1273) was acidified with sulphuric acid, 4 drops of indicator were added, and the solution was titrated with 0·1N-ceric sulphate solution (*ibid.*). Titrations were also carried out in the presence of phosphoric acid.

(III) *Preparation of* N-*Ethylbenzidine.*—4-Amino-4′-nitrodiphenyl (8 g.) (for preparation, see *J.*, 1953, 1336) was dissolved in acetone (50 ml.), and ethyl iodide (15 g.) added. The mixture was sealed in a glass tube and warmed for 3 hr. in a boiling-water bath. The tube was cooled and opened, and the contents were poured into water. Ethyl iodide and acetone were removed by distillation, and the residue was made alkaline and filtered. The orange-red solid was washed well with water, drained, and oven-dried (80°). It was recrystallised from acetone, forming large, orange-red, glistening plates (5 g.), m. p. 168°.

This amine (5 g.) was suspended in ethanol (50 ml.), concentrated hydrochloric acid (10 ml.) was added, and the mixture was boiled under reflux. Zinc dust (12 g.) was added in small portions to the boiling solution (15 min.), and the almost colourless solution was refluxed for a further 30 min. The ethanol was distilled off, and the residue made alkaline. The liberated base was extracted with ether, the ether evaporated off, and the remaining semi-solid material recrystallised from methanol. The base formed very pale yellow prisms (3 g.), m. p. 85°. The hydrochloride and sulphate were isolated only with difficulty.

Chemistry Department, The University,
Edgbaston, Birmingham, 15.

[*Received, February 8th*, 1954.]

The Cyanogen Halides. Part III. Their Heats of Formation and Free Energies.*

By G. Lord and A. A. Woolf.

[Reprint Order No. 5129.]

The heats of formation of the cyanogen halides have been determined by measuring the sum of the heats of alkaline hydrolysis of cyanogen and of the cyanogen halides, and the heat of reaction of iodine with an alkali cyanide. The values for cyanogen chloride, bromide, and iodide in their standard and gaseous states at 25°, the heat of sublimation of the bromide (found from the redetermined vapour-pressures), and the free energies in the gas phase at 25° (from the recalculated entropies) are reported. The dissociations to molecules, atoms, and ions are discussed.

The heats of formation and free energies of the cyanogen halides are required, first to confirm that cyanogen bromide and iodide are really as metastable with respect to cyanogen and the halogens as the old data imply, especially in view of the ready equilibration of the nitrosyl and interhalogen halides; secondly, to see whether the free energy of cyanogen bromide is the mean of those for the chloride and iodide as assumed in Part I *; thirdly, for the determination of the heats of formation of the double halides described in Part II.* By comparing these heats with those of the corresponding ionic nitrosyl compounds it is hoped to draw some conclusions about the bonding in the cyanogen complexes.

Since all previous data depend to some extent on Berthelot's values (*Ann. Chim. Phys.*, 1875, **5**, 455), these have been redetermined where necessary. The heats of the alkaline hydrolyses, $CNX + 2NaOH = NaCNO + NaX + H_2O$ (X = Cl, Br, or I) have been measured, and the stoicheiometry of this reaction has been established for cyanogen bromide and iodide, where there had been some doubt (Migrdichian, "Organic Cyanogen Compounds," Reinhold Publ. Corp., N.Y., 1947, p. 101; Williams, "Cyanogen Compounds," Arnold and Co., London, 1948, p. 9).

There is a possibility of considerable error in the heat of formation of sodium cyanate found by Lemoult (*Ann. Chim. Phys.*, 1899, **16**, 338) from the heat change on acid hydrolysis, because of the difficulty of complete retention, or expulsion, of carbon dioxide from the hydrolysate. An alternative procedure, in which the recently determined heat of formation of cyanogen (Knowlten and Prosen, *J. Res. Nat. Bur. Stand.*, 1951, **46**, 489) is used, involves the heats of the reactions $NaCN + I_2 = NaI + ICN$, $ICN + 2NaOH = NaCNO + NaI + H_2O$ and $C_2N_2 + 2NaOH = NaCNO + NaCN + H_2O$. Their sum enables the heat of formation of sodium cyanate to be determined. A value for sodium cyanide can also be derived.

To obtain the heats of formation of cyanogen bromide and iodide in the gas phase, the respective heats of sublimation are required. Two values have been recorded for the latter and are given equal weight (Yost and Stone, *J. Amer. Chem. Soc.*, 1933, **55**, 1889; Ketelaar and Kruyer, *Rec. Trav. chim.*, 1943, **62**, 550). Only one value for cyanogen bromide is available (Baxter, Bezzenberger, and Wilson, *J. Amer. Chem. Soc.*, 1920, **42**, 1368) so the vapour pressure has been redetermined. The entropies of the cyanogen halides, calculated by Stevenson (*J. Chem. Phys.*, 1939, **7**, 171), have been redetermined in view of the accurate bond-length data now available, as well as the small changes in fundamental constants.

Experimental

The calorimeter was similar to that described previously (Woolf, *J.*, 1951, 231). In the electrical calibration, the heater resistance was determined on a standardized Wheatstone bridge, and the applied e.m.f. on a vernier potentiometer. All measurements, with the inclusion of chemical analysis, were made to within 0·2%. Care was taken to bring the calorimeter and contents to temperature equilibrium before and after heat changes. The cyanogen halides were prepared, and purified shortly before use, by the methods described in Part I (*loc. cit.*).

* Part I, *J.*, 1953, 4121; Part II, *J.*, 1954, 252.

Heat of Hydrolysis of Cyanogen Halides.—(i) *Chloride.* An evacuated glass bulb (250 ml.) fitted radially with two taps was filled with cyanogen chloride almost to atmospheric pressure at room temperature (18—20°). The amount of gas was found by direct weighing. One side was connected to a mercury reservoir, the other to an inlet tube terminated by a sintered disc (2·5 cm. diam., no. 2 porosity) and immersed just below the stirrer in 500 ml. of 0·5N-sodium hydroxide. After equilibration at 25° both taps were opened, and the gas was forced into the alkali by raising the mercury reservoir. The gas was expelled within 1½ min. and the heat rise was completed within 2 min. Calibration was effected after the heat rise due to stirring was again uniform. The solution which remained was analysed for chloride, since only about 98% of the gas was hydrolysed under the above conditions. This was not due to the rate of hydrolysis (Eden and Wheatland, *J. Soc. Chem. Ind.*, 1950, **69**, 166) or to the non-stoicheiometry of the reaction (Douglas and Winkler, *Canad. J. Res.*, 1947, **25**, *B*, 381) but to the failure to absorb gas at the high rate of flow employed. A finer sinter, or slower rate, would have ensured more complete absorption.

(ii) *Bromide.* Powdered cyanogen bromide, obtained by distillation *in vacuo* to liquid-air temperature, was placed in a weighed, thin-ended tube, the other end of which was ground flat and closed with a cover-slip and picein wax. After a reweighing, the tube was immersed in 500 ml. of N-sodium hydroxide and pierced with a pointed rod when a steady state had been attained.

The stoicheiometry was checked in separate experiments by estimation of cyanate and bromide formed. The absence of cyanide, bromate, and hypobromite was shown by qualitative tests. This confirms Moeller's results (*Kgl. Danske Videnskab. Selsk.*, 1934, **12**, 17).

(iii) *Iodide.* The iodide, which could not be powdered, was weighed into a glass tube whose ends were closed with rubber bungs. This was held at 25° in the thermostat before the bungs were removed and the rest dropped into the alkali. The iodide adhering to the bungs was estimated by titration of the iodide formed with standard iodate (Andrews's method). In these reactions the maximum temperature was obtained after about 20 min., compared with about 1 min. with cyanogen bromide. The observed times are in agreement with values calculated from hydrolysis rates. [A large excess of hydroxide is used so that its concentration is approximately constant, and the rate law is pseudo-unimolecular. The reaction is 99·9% complete in ten half-life periods and this is numerically equal to $10 \log_e 2/k[\mathrm{OH}]$, where k is the velocity constant. At 25°, k is approx. 0·3, 50, and 530 for cyanogen iodide, bromide, and chloride, respectively (Griffith and McKeown, *Trans. Faraday Soc.*, 1938, **34**, 316; Eden and Wheatland, *loc. cit.*), so the time of hydrolysis in normal alkali is 23, 0·14, and 0·013 min., respectively.] The results for alkaline hydrolyses are tabulated, ΔT being the rise in temperature. The water equivalent is the heat (in cal.), determined electrically, to raise the calorimeter and contents by 1°. The quantities of cyanogen bromide and iodide were determined by direct weighing, those of cyanogen chloride by analyses.

Water equiv. (cal./°)	ΔT	Wt. (g.)	Heat/mole (kcal.)	Water equiv. (cal./°)	ΔT	Wt. (g.)	Heat/mole (kcal.)
CNCl in 500 ml. of N/2-NaOH.							
532·5	1·387°	0·685 [1]	66·29	533·3	1·353	0·671	66·11
532·9	1·458	0·719	66·43	534·6	1·412	0·699	66·39
535·9	1·381	0·685	66·41			Mean 66·3(3) ± 0·10	
CNBr in 500 ml. of N-NaOH.							
541·4	0·974°	0·9994	55·89	539·4	0·979°	0·9940	56·27
539·0	0·941	0·9588	56·04	540·8	1·000	1·0279	55·73
541·2	0·929	0·9450	56·36			Mean 56·0(6) ± 0·17	
543·2	0·950	0·9746	56·08				
ICN in 500 ml. of N-NaOH.							
539·4	0·823°	1·466 [2]	46·28	539·5	0·845°	1·500	46·46
538·4	0·852	1·517	46·23	537·4	0·862	1·529	46·33
540·0	0·843	1·498	46·44			Mean 46·3(5) ± 0·08	

[1] The percentage of CNCl utilized was 97·4, 96·8, 98·2, 95·6, 98·4, respectively. Gravimetric and volumetric analyses agreed to the last figure. [2] Weight of ICN as determined by Andrews's titration of iodide, 1·465, 1·515, 1·496, 1·500, 1·529 g., respectively.

Heat of Formation of Sodium Cyanate.—(1) *By acid hydrolyses.* Sodium cyanate (20 g.) was recrystallised from methanol–water (2 : 1) (600 c.c.), giving 8 g. of pure cyanate, and because of

its bulky nature this was compressed into pellets. About 1 g. of cyanate (2 or 3 pellets) was dropped into 500 ml. of water, and the heat of solution measured. N-Hydrochloric acid (38 ml.) was then added by piercing an ampoule suspended in the cyanate solution, and the heat of hydrolysis was measured. The acid normality at the end was 0·02N and it was assumed that all carbon dioxide remained in solution. In another type of experiment sodium cyanate pellets were added to a large excess of N-sulphuric acid. The assumption here was that all carbon dioxide was eliminated. There was a pronounced hump, corresponding with the cooling caused by evolution of carbon dioxide gas, in the time–temperature curves of the latter experiments. The heat of solution of sodium cyanate in N-sodium hydroxide was also determined.

An attempt to determine the carbon dioxide was only semi-quantitative because of its loss during transfer of the 80—90% saturated solutions. The solution was acidified, and the dioxide steam-distilled into excess of baryta, which was then back-titrated with acid. Equivalent solutions were employed with sodium carbonate in place of cyanate. About 74% of the carbon dioxide was found after 7 min. (the time for the mid-point of the temperature rise) which decreased to 53% after 42 min. Although the absolute values were not significant, the demonstration of a loss of gas under the experimental conditions was important. A 10% loss corresponds to 0·4 kcal. An estimation under the conditions of the sulphuric acid experiments showed that some carbon dioxide was retained. It can only be concluded that the agreement between the methods must be due to a cancellation of errors. The results were as follows:

NaCNO in 500 ml. of N-H_2SO_4: Heat/mole, 22·85, 22·79, 22·76; mean 22·8(0) ± 0·03.
NaCNO in 500 ml. of H_2O: Heat/mole, −4·62, −4·67; mean −4·64 ± 0·03.
Addition of 38 ml. of N-HCl: Heat/mole, 27·51, 27·74; mean 27·6(2) ± 0·10.
NaCNO in 500 ml. of N-NaOH: Heat/mole, −4·54, −4·52; mean −4·53 ± 0·01.

(2) *By the cyanogen route.* (i) Heat of reaction of iodine with alkali cyanides. Powdered iodine was added to excess of sodium cyanide solution in this series of experiments. The heat of solution of cyanogen iodide in a solution of the same concentrations of sodium iodide and cyanide as that left after the reaction, was determined separately:

500 ml. of 6% NaCN solution + 19 g. of iodine: Heat/mole, 9·04, 9·08, 9·11, 9·09, 9·07, 9·12; mean 9·09 ± 0·02.
ICN in NaCN + NaI solution: Heat/mole, −1·29, −1·25, mean −1·27 ± 0·02.
The corresponding figures for potassium cyanide were 8·69, 8·73, 8·77, 8·73, 8·78 (mean 8·74 ± 0·03) and −1·33.

(ii) Heat of hydrolysis of cyanogen. The cyanogen, prepared by heating dry silver cyanide at 360° *in vacuo*, was purified by fractionation *in vacuo*. It was hydrolysed in the same way as cyanogèn chloride, and the hydrolysate analysed, because of incomplete absorption (98·2 ± 0·4% of the gas reacted in these experiments). The cyanide was determined by the Liebig–Denigès method, and the total cyanide and cyanate by Volhard's procedure. The latter results, all about 0·5% low because of the appreciable solubility of silver cyanate, were used as a rough check on the stoicheiometry of the hydrolysis. The results were:

C_2N_2 in 500 ml. of 0·1N-NaOH. Mean water equiv. 530·0 ± 1·1 cals./°C.

Wt. of C_2N_2 (g.)	Temp. rise	Heat/mole (kcal.)	Wt. of C_2N_2 (g.)	Temp. rise	Heat/mole (kcal.)
0·586	0·703°	33·10	0·577	0·689	32·95
0·582	0·700	33·19	0·582	0·701	33·21
0·583	0·695	32·89		Mean 33·0(5) ± 0·12	
0·580	0·693	32·95			

The heat of formation of solid sodium cyanate calculated from the experiments with sulphuric acid is −97·1, the following heats of formation being used: −211·50 for H_2SO_4, 331·2 for $(NH_4)_2SO_4$, −280·1 for Na_2SO_4, and −94·05 for carbon dioxide gas. The experiments in hydrochloric acid give −92·5 for the aqueous heat of formation using −39·6 for HCl, −71·7 for NH_4Cl, and −98·7 for aqueous carbon dioxide. The difference between these figures, *viz.*, 4·6, agrees with the determined heat of solution.

The heat of formation of sodium cyanate calculated from the cyanogen route is −98·1 for the solid and −93·4(5) for the aqueous solution. The heats involved are: C_2N_2, 73·84; NaOH, −112·15; H_2O, −68·3; heat of solution of CNI, −1·27, and the heat of dilution of NaCN (45—4800 mols. of H_2O). Direct measurement of the last gave approximately 0·06, but a value of 0·1, the figure for the heats of dilution of the other sodium halides, was used.

The heats of formation of sodium cyanide from these data are $NaCN_c$ −21·4 and NaCN(135 H_2O) −21·85; for aqueous potassium cyanide, −25·05 is found from the difference in the heats of reaction of iodine with potassium and sodium cyanides.

The heats of formation of cyanogen chloride, bromide, and iodide were calculated to be 31·6, 32·5, and 38·3 in their standard states, the following heats of formation being used: NaCl −97·24, NaBr −86·12, NaI −70·59, NaCNO −93·4. In the gas phase the heats of formation became 43·3 and 52·4 for cyanogen bromide and iodide; the latent heats of sublimation were taken as 10·8 and 14·1, respectively.

Vapour Pressure of Cyanogen Bromide.—This was determined statically by means of a mercury manometer. (It has already been shown that mercury is only slowly attacked by molten cyanogen bromide; Part I, *loc. cit.*). The manometer and cyanogen bromide bulb were filled by the usual vacuum technique and then kept in a thermostat at various temperatures. Between each reading the cyanogen bromide bulb was cooled in liquid nitrogen to recondense any cyanogen bromide which had distilled on to the glass surfaces. All measurements were made with respect to a reference mark on the mercury limb unexposed to bromide vapour. The results (T in °K and p in terms of mm. of Hg at 0°) are given below; the last three were obtained after an interval of 3 days at room temperature. The manometer could still be read after a month. With less carefully purified specimens, attack was appreciable after a few days.

T ...	273·3	284·5	288·2	288·8	291·5	293·3	298·3	303·0	303·5	308·6	313·1	289·0	298·2	308·2
p	22·2	49·3	63·8	66·0	77·6	89·8	120·0	159·8	163·6	221·8	281·8	65·8	119·0	216·0

The vapour pressure equation is $\log_{10}p = 9{\cdot}993 - 2{\cdot}360/T$; the latent heat of sublimation 10·8(1) kcal.

Entropies.—The entropies are only required to a slightly higher accuracy than the heats of formation (0·1 kcal.). Smith, King, Smith, and Gordy's bond lengths (*Phys. Review*, 1948, **74**, 370) have been used. The more recent data for cyanogen bromide and iodide hardly affect these values (Simmons and Anderson, *ibid.*, 1950, **80**, 338; Tetenbaum, *ibid.*, 1952, **86**, **444**). The entropy values are given in the order CNCl, CNBr, CNI: translational entropy, 38·256, 38·877, 40·972; rotational, 15·800, 16·532, 17·014; vibrational, 2·222, 2·663, 3·349. Total entropy, 56·28, 59·07, 61·33 (Stevenson, *loc. cit.*, gave 54·72, 58·26, 60·76).

The only source of appreciable error in this determination is in the uncertainties of the fundamental frequencies. West and Farnsworth's data (*J. Chem. Phys.*, 1933, **1**, 402) are used. Wagner's more recent values (*Z. physikal. Chem.*, 1941, *B*, **48**, 309; 1943, *A*, **193**, 55), which differ by 11 wave-numbers in the worst instance, would give a difference of less than 0·05 kcal. in the free energies at 25°, compared with 0·46 kcal. obtained with Stevenson's figures.

The free energies of gaseous cyanogen chloride, bromide, and iodide at 298·2°K, calculated from the entropy and thermal data, are 30·0, 38·3, and 45·5, respectively. The value for the bromide is within 1 kcal. of the mean of the other two.

Discussion

The heat of formation of cyanogen chloride was determined by Berthelot (*loc. cit.*) from the heat of its alkaline hydrolysis at 21°. The cyanogen chloride was introduced in the liquid state, so the heat of vaporization was required. His figure of 8·76 kcal. was higher than more recent values (Cook and Robinson, *J.*, 1935, 1001, 6·36 kcal.; Douglas and Winkler, *Canad. J. Res.*, 1947, **25**, *B*, 381, 6·40 kcal.). In the procedure described, which resulted in a more rapid reaction, the heat of formation of the gas was measured directly at 25°.

The heat of formation of cyanogen bromide has not been recorded, although Berthelot attempted to use the reaction of bromine with a cyanide. The secondary reaction of cyanogen bromide and the cyanide interfered.

Values for cyanogen iodide have been measured by two methods. Berthelot found the heat of reaction of iodine with potassium cyanide solution at 20° to be 6·3 kcal. Our value obtained at 25° is 8·74 ± 0·03 kcal. (This reversal of values compared with the latent-heat figures is probably coincidental.) A measure of the free energy of cyanogen iodide was determined from an approximate equilibrium constant for $ICN + H^+ + I^- \rightleftharpoons HCN + I_2$ (Lewis and Keys, *J. Amer. Chem. Soc.*, 1918, **40**, 472). Yost and Stone (*ibid.*, 1933, **55**, 1889) obtained a more consistent value from Kovach's results (*Z. physikal. Chem.*, 1912, **80**,

107) corrected for the formation of complex ions, $I(CN)_2^-$ and I_2CN^-. Gauguin has estimated the equilibrium constant from measurements on the redox potential of the CN^-–I_2 couple (*Bull. Soc. chim.*, 1948, 1048). Values of the free energy calculated from these data depend on the heat of formation of hydrogen cyanide determined by Berthelot and Thomsen. The free energies found in this work are independent of the old thermochemical data and are reliable to 0·6 kcal. The main errors are in the heat of formation of cyanogen, the heats of sublimation of cyanogen iodide and bromide, and in the measured heats of reaction.

The dissociations of cyanogen halides to halogens and cyanogen, expressed as $\log_{10} K$, where K is the equilibrium constant, are −4·0(3), 1·7(6), and 5·5(6) for the chloride, bromide, and iodide, respectively, in the gas state. Thus cyanogen chloride at equilibrium is less dissociated than nitrosyl chloride ($\log_{10} K = -3{\cdot}57$), and the metastability of cyanogen iodide is as great as the old figures indicate. It has already been emphasized by Yost and Stone (*loc. cit.*) that the gaseous iodide does not equilibrate so that dissociation measurements yield false values for the free energy.

The carbon–halogen bond-dissociation energies, the heat of reaction for CNX = CN + X, can be given greater precision because of recent values for the heat of formation of the cyanogen radical. Two independent methods lead to values of 94·3, and 92·7 ± 6 kcal. (Brewer, Templeton, and Jenkins, *J. Amer. Chem. Soc.*, 1951, **73**, 1462; McDowell and Warren, *Trans. Faraday Soc.*, 1952, **48**, 1084). The dissociation energies for cyanogen chloride, bromide, and iodide are 91·4, 77·4, and 67·1 ± 7 kcal. if the heat of formation of cyanogen radical is 94 kcal. These energies have been measured by observations on the absorption limit in the ultra-violet spectra (Badger and Woo, *J. Amer. Chem. Soc.*, 1931, **53**, 2573; Mooney and Reid, *Proc. Roy. Soc. Edin.*, 1932, **52**, 152). From their mean wave-length limits, and an excitation energy of 26·4 kcal. for the excited cyanogen radical formed in the photodissociation, the dissociation energies are 102, 88, and 69 kcal. These are maximum values because the experimental wave-length limits are only rough minimum values. Recently Stevenson (*J. Chem. Phys.*, 1950, **18**, 1347) has used the electron-impact method to obtain possible values for the dissociation energy of cyanogen chloride, which however depend on the state of the cyanogen radical formed in these experiments (compare McDowell and Warren, *loc. cit.*).

The heats of formation of cyanogen halides from cyanogen and halogens in the gas phase are equal to Pauling's ionic resonance energies if the cyanogen radical can be considered equivalent to a halogen atom. Only for cyanogen chloride is the reaction exothermic (+5·3 kcal.), and the derived electronegativity coefficient, 2·5, implies that the cyanogen radical is close to iodine. The heats of formation for cyanogen bromide and iodide, −2·7 and −8·1 kcal., show that there is no stabilization by covalent-ionic resonance. However, it is doubtful whether the simple electronegativity ideas are applicable to the cyanogen or nitrosyl halides. (For nitrosyl chloride and bromide, the derived coefficients of 2·4 and 2·3 respectively, would lead to a large electron affinity for the nitrosyl radical.)

For a series of related molecules there is usually some connection between bond energy and length. In the simplest instance contraction in length is associated with a strengthening of the bond. The bond contraction for carbon–halogen double bonds compared with single bonds are all 0·18—0·20 Å (Bernstein, *J. Chem. Phys.*, 1947, **15**, 285). The bonds in cyanogen chloride, bromide, and iodide are respectively 0·13, 0·12, and 0·10 Å less than single bonds. [The variation of carbon–nitrogen distance in these molecules shows a barely perceptible movement in sympathy (Smith *et al.*, *loc. cit.*) but the constancy of bond length to within ±0·01 Å in the cyanogen radical when joined to groups as diverse as H, CH_3, CN, Cl, Br, and I is remarkable.] One would expect this contraction to be reflected in an increasing bond strength from the iodide to chloride. The carbon–halogen bond dissociation energies for normal single bonds are taken as 81, 68, and 53 ± 2—3 kcal., the mean of values for alkyl halides (Lane, Linnett, and Oswin, *Proc. Roy. Soc.*, 1953, *A*, **216**, 361); the bond strength in cyanogen halides, i.e., the heats of dissociation CNX = CN + X, is therefore enhanced by 10·5, 9·8, and 14·0 kcal. as compared with the single bond energies. The carbon–iodide bond is strengthened by more than the carbon–chlorine bond. It may well be that this contradiction arises from errors in the heats of dissociation, although the largest

uncertainty, that in the heat of formation of the cyanogen radical, is eliminated when the cyanogen halides are treated as a group.

The dissociation of cyanogen halides into ions can also be calculated. The real interest is in the dissociation in solution, but unfortunately no data for the solvation energies of positive halogen or cyanogen ions are available unless assumptions are made about ionic radii in solution. In the gas phase the heats of formation of positive and negative cyanogen ions are uncertain. The electron affinity of cyanogen is very near that of bromine. Various methods yield a value of 83 kcal. (Pritchard, *Chem. Reviews*, 1953, **52**, 529) and hence the heat of formation of the cyanide ion is 11 kcal., 94 kcal. being used for the cyanogen radical. The ionization potential of the cyanogen radical is assumed to be not less than that of bromine atom (275 kcal.) [Stevenson's value of 335 kcal. (*loc. cit.*) is probably high because the cyanogen radical formed in his experiments may have excess of kinetic energy.] This leads to a heat of formation for the positive cyanogen ion of 369 kcal. and the following heats of reaction :

$$CNCl \longrightarrow CN^+ + Cl^-,\ -278; \quad CNCl \longrightarrow CN^- + Cl^+,\ -307.$$
$$CNBr \longrightarrow CN^+ + Br^-,\ -270; \quad CNBr \longrightarrow CN^- + Br^+,\ -268.$$
$$CNI \longrightarrow CN^+ + I^-,\ -266; \quad CNI \longrightarrow CN^- + I^+,\ -226.$$

Hence, for cyanogen iodide but not for the chloride, the ionization to a positive cyanogen ion and a halide ion is more endothermic than to a positive halogen ion and a cyanide ion : there is little difference for cyanogen bromide. Because of the uncertainty in the ionization potential of cyanogen radicals the only certain conclusion, however, is that the heat of reaction $X^- + CN^+ \longrightarrow X^+ + CN^-$ becomes progressively more endothermic from cyanogen chloride to iodide.

The minuteness of the ionization of cyanogen halides in aqueous solution is also demonstrated by the above figures. The solvation energy for cyanogen halides may be assumed to be of the same order as those of the alkali halides since the sizes of the positive halogen ions are approximately those of the alkali cations. Thus the maximum solvation energy available is only about 190 kcal. and the ionizations in solution would still remain considerably endothermic. The extent of ionization would appear to increase from chloride to iodide and it seems likely that the apparently greater ionization of cyanogen chloride is due to its more rapid hydrolysis rather than to a primary ionization.

The mechanism of alkaline hydrolysis of cyanogen chloride may differ from that of cyanogen iodide, although the stoicheiometry is the same for both reactions. This point will be discussed in Part IV.

The authors are grateful to Dr. F. Fairbrother for his advice during this work, which was carried out whilst one of the authors (A. A. W.) was a Turner and Newall Fellow.

MANCHESTER UNIVERSITY. [*Received, February 16th*, 1954.]

The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part IV. The Dipole Moments of the 2 : 2′-Dihalogeno- and 2 : 2′- and 3 : 3′-Dinitro-diphenyls.*

By A. C. Littlejohn and J. W. Smith.

[Reprint Order No. 5170.]

The dipole moments of 2 : 2′-difluoro-, -dichloro-, -dibromo-, -di-iodo- and -dinitro-diphenyl and of 3 : 3′-dinitrodiphenyl have been determined in benzene solution at 25°. On the assumption that the primary moments of the substituent groups, and the induced moments which they produce in the rings in which they are present, are the same as in the monosubstituted benzenes, the moments induced by each substituent in the opposite ring and in the other substituent have been calculated for various angles of inclination of the planes of the rings. It is found that, so long as the rings are coaxial, the observed moments of the 2 : 2′-disubstituted diphenyls are in accord with the calculated values only if the substituent groups have a preferred slightly-*cis*-disposition. For 3 : 3′-dinitrodiphenyl the dipole moment value suggests preference for a slightly-*trans*-configuration. These conclusions hold over all reasonable ranges of the location of the dipole and are in qualitative accordance with electron-diffraction measurements.

Interest in the dipole moments of the 2 : 2′-disubstituted derivatives of diphenyl centres around the fact that the *cis*-coplanar configuration and a wide range of orientations of the planes of the rings around this relative position are precluded on steric grounds. Further, it has been found that compounds which depend for their enantiomorphism on interference between 2 : 2′-substituents and the 6- and the 6′-hydrogen atom can be resolved when the 2 : 2′-substituents are iodine or bromine atoms (2 : 2′-di-iodo- and 2 : 2′-dibromo-diphenyl-4 : 4′-dicarboxylic acids; Searle and Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 1649; 1934, **56**, 2112), though the active forms are of relatively low optical stability. No optical activity has been observed, however, in analogous compounds containing 2 : 2′-dichloro- or difluoro-substituents. It may be inferred, therefore, that the *trans*-coplanar configuration also involves a much higher potential energy than the orthogonal configuration, a view which was supported by dipole-moment measurements on the 2-monosubstituted derivatives (Part II, *J.*, 1953, 2456). It would be expected, therefore, that the mean configuration of the rings in the 2 : 2′-disubstituted compounds would be not far removed from the orthogonal arrangement, but rather nearer to the *trans*- than to the *cis*-position.

It was shown by Hampson and Weissberger (*J. Amer. Chem. Soc.*, 1936, **58**, 2111), however, that the dipole moment of 2 : 2′-dichlorodiphenyl is greater than that of the 3 : 3′-isomeride. The difference between the moment observed for the latter (1·80 D) and the value calculated for free rotation on the assumption that the group moment is the same as in chlorobenzene (1·90 D) was attributed to induction effects, and these authors suggested that the higher value for 2 : 2′-dichlorodiphenyl (1·91 D) was due to London forces acting in such a manner as to maintain the mean configuration of the molecule as a *cis*-arrangement, with the rings in planes inclined at about 62°. Further, from electron-diffraction measurements on the vapours, Bastiansen (*Acta Chem. Scand.*, 1950, **4**, 926) has found that the mean angle between the planes of the rings is 74°, 75°, and 79° in 2 : 2′-dichloro-, 2 : 2′-dibromo-, and 2 : 2′-di-iodo-diphenyl, respectively, with halogen atoms *cis* to one another in each case. Again, *X*-ray crystal analysis has shown that in the solid state the inter-planar angles are 72° in 2 : 2′-dichlorobenzidine (Smare, *Acta Cryst.*, 1948, **1**, 150) and 71° in 2 : 2′-dimethylbenzidine dihydrochloride (Fowweather and Hargreaves, *Acta Cryst.*, 1950, **3**, 81), the 2 : 2′-groups having a *cis*-disposition in each case.

In view of this evidence it was of interest to study the dipole moments of a wider range of 2 : 2′-disubstituted diphenyls, in order to ascertain whether this preferential *cis*-disposition is general, irrespective of the size and nature of the substituent group. As

* Part III, *J.*, 1954, 131.

they give rise to dipoles which are symmetrically disposed with respect to the ring in which they are substituted, thereby facilitating interpretation of the results, the halogen atoms and nitro-group were selected as substituents in this investigation. In view of Hampson and Weissberger's observations on the relative values of the moments for 2 : 2′- and 3 : 3′-dichlorodiphenyl, it was also of interest to compare the moment of 3 : 3′-dinitrodiphenyl with that of the 2 : 2′-isomer.

The results are summarised in Table 1, where α, β, and ν are the limiting values of $d\varepsilon/dw$, dv/dw, and dn^2/dw, respectively, and the other symbols have their usual significance.

TABLE 1. *Polarisation data for solutions in benzene at* 25°.

Diphenyl derivative	$10^3\alpha$	$-10^4\beta$	$10^3\nu$	$P_{2\infty}$ (c.c.)	$[R_D]$ (c.c.)	μ(D)	Previous values
2 : 2′-Difluoro-	2,120	3209	127	122·5	50·5	1·88	
2 : 2′-Dichloro-	2,095	3586	230	141·2	61·2	1·97	1·72,[a] 1·77,[b] 1·91[c]
2 : 2′-Dibromo-	1·460	5614	222	140·0	66·5	1·90	
2 : 2′-Di-iodo-	1,006	6633	232	135·0	74·9	1·71	
2 : 2′-Dinitro-	11,785	4304	244	593·3	62·5	5·10	5·12,[a] 5·19[d]
3 : 3′-Dinitro-	7,950	4387	226	416·5	61·1	4·17	

[a] Bretscher, *Helv. Phys. Acta*, 1929, **2**, 257. [b] Weissberger and Sängewald, *Z. physikal. Chem.*, 1933, **20**, *B*, 145. [c] Hampson and Weissberger, *J. Amer. Chem. Soc.*, 1936, **58**, 2111. [d] Le Fèvre and Vine, *J.*, 1938, 967.

Before these dipole-moment values can be applied in calculating the mean angle of inclination between the planes of the rings, correction must be made for inductive effects which need not be of the relatively secondary importance often ascribed to them. Their magnitudes vary with the angle between the planes of the rings, but, by applying the method used in Part II, they can be evaluated as functions of this angle ϕ.

These compounds differ from the monosubstituted derivatives studied previously in that they must be regarded as derived from the mono-derivative of benzene, not only by replacement of a hydrogen atom by a second benzene ring, but also by the introduction of a second substituent group. The inductive effects can therefore be regarded as comprising (i) the effects already present in the monosubstituted benzene, (ii) the effects of each dipole on the second ring, and (iii) the moment induced at each dipolar substituent by the presence of the other.

The inductive effect produced by each dipole in the opposite benzene ring is similar to that in the 2-monosubstituted diphenyl. From the geometry of the molecule, and the consideration that the polarisability of benzene at right angles to the plane of the ring is half of that in the plane of the ring, it follows that if effects (i) and (ii) only were present the moment should be given by

$$\mu = \left\{\sqrt{3}\,\mu_{PhX} + (\mu_y - \sqrt{3}\,\mu_x)\cos^2\frac{\phi}{2}\right\}.\cos\frac{\phi}{2} \quad . \quad . \quad . \quad . \quad (1)$$

where μ_{PhX} is the moment of the corresponding mono-derivative of benzene, and μ_x and μ_y are the induced moments produced at the centre of each ring, respectively parallel with and at right angles to the dipole in the other ring, when the rings are coplanar.

The method of evaluating μ_x and μ_y was discussed in Part II. There it was assumed that the point of action of the dipole was at the " point of contact " of the carbon and the halogen atom in the halogeno-derivatives and at the centre of the nitrogen atom in the nitro-compounds. Although the precise location of the dipole does not affect the arguments then advanced regarding the configurations of the mono-derivatives, these positions are probably rather too near to the centre of the benzene ring. On classical views the effective centre of the dipole must be located at some point between the position previously assumed and the polarisable centre of the substituent, whilst the present view that the moment in such halogeno-derivatives arises principally from the asymmetry of the non-bonding orbitals suggests that it cannot be far removed from the polarisable centre. Hence, in the present series of calculations the induced moments have been evaluated for these two extreme positions of the dipole and also for the dipole half-way between these

positions. The following inter-nuclear distances have been used in calculating r (the distance between the dipole and the polarisable centre) and θ (the angle between r and the axis of the dipole): C–C (aromatic) 1·40, C–C (centre bond) 1·50, C–N 1·45, C–F 1·495, C–Cl 1·765, C–Br 1·885, and C–I 2·105 Å.

The evaluation of the moment induced in one polar substituent by the presence of the other involves a knowledge of the polarisability of the substituent, its dielectric constant, the distance between each inducing dipole and the polarisable centre of the other substituent group, and the angle between the direction of the inducing dipole and the line from its point of action to the polarisable centre. The last two vary with ϕ, but the geometry of the problem does not permit the evaluation of the effect as a general function of this angle, so it is necessary to calculate the mutual polarisation effect for various values of ϕ, and to combine this result with the moment expected from consideration of the primary dipoles and ring induction only, as given by equation (1), so as to obtain "theoretical" dipole moment values for these different values of ϕ. The results so obtained can be compared with the observed moment and the angle between the planes corresponding with the latter deduced.

The following values, deduced from molecular refraction data, of the differences between the polarisabilities of the substituent groups and that of the hydrogen atom have been used in these calculations: F 0, Cl 1·91, Br 3·05, I 5·07, and NO_2 2·24, all $\times 10^{-25}$ c.c., respectively. The effective dielectric constant of the group is more difficult to decide, but, since this occurs in a term $(\varepsilon + 2)$ only, no great error can be introduced by using the value for carbon tetrachloride (2·23).

The results of the introduction of these inductive effects are shown in Table 2. Column 4 gives the values of the angle between the planes of the rings if all induction effects are ignored; columns 5, 6, and 7 give the angles deduced for the three positions of the dipole if induction in the rings only is considered, and columns 8, 9, and 10 the corresponding angles when the mutual induction between the polar groups is also included.

TABLE 2. *Mean angles between planes of rings in disubstituted compounds.*

Diphenyl derivative	μ (D) observed	μ_{PhX} (D)	Mean angle between planes of rings: No allowance for induction	Corrected for induction in rings only: *a*	*b*	*c*	Corrected for induction in rings and polar groups: *a*	*b*	*c*
2 : 2′-Difluoro- ...	1·88	1·48	86°	71°	79°	74°	71°	79°	74°
2 : 2′-Dichloro- ...	1·97	1·58	88	75	84	80	69	82	75
2 : 2′-Dibromo- ...	1·90	1·56	90	79	88	84	68	85	77
2 : 2′-Di-iodo- ...	1·71	1·40	90	78	90	85	50	84	69
2 : 2′-Dinitro- ...	5·10	4·01	86	78	84	81	72	80	76
3 : 3′-Dinitro- ...	4·17	4·01	106	105	105	105	105	105	105
3 : 3′-Dichloro- ...	1·80 *	1·58	98	97	97	97	97	97	97

a, Dipole located at "point of contact" of carbon and halogen atom or centre of nitrogen atom. *b*, Dipole located at polarisable centre of substituent group. *c*, Dipole located mid-way between positions *a* and *b*.

* Hampson and Weissberger, *loc. cit.*

After all inductive effects have been taken into account the calculated angle ϕ varies most systematically with the size of the substituent group when the dipole is assumed to be located at the polarisable centre of the substituent group, although whatever assumption is made the mean angles found for the 2 : 2′-disubstituted compounds are less than 90°, *i.e.*, the groups have a slightly-*cis*-disposition. If, as is most probable, the dipole is effectively located near the polarisable centre of the substituent, the angle increases slightly from 2 : 2′-difluoro- to 2 : 2′-dibromo- and 2 : 2′-di-iodo-diphenyl. At an inclination of 79°, as is indicated for 2 : 2′-difluorodiphenyl, the overlap between the π-orbitals of the two rings would be expected to be small, but this overlap disappears completely only at 90°. Hence we would expect that, if the estimates of the inclinations between the ring planes are quantitatively reliable, there might be a very slight conjugation between the rings in the 2 : 2′-difluoro- and 2 : 2′-dinitro-compounds, but that this conjugation would be diminished

in 2 : 2′-dichlorodiphenyl and become very small indeed in 2 : 2′-dibromo- and 2 : 2′-di-iodo-diphenyl. The ultra-violet absorption evidence for conjugation in the 2 : 2′-di-halogeno-compounds will be discussed in Part V.

The reason for the preferred *cis*-orientation is not obvious For a system of dipoles such as are present in these compounds it can be shown that the mutual dipolar potential energy is a minimum when the angle between the planes of the rings is between 70° and 80°, but the depth of this potential energy well is so small that it cannot affect the mean configuration of the molecules appreciably at 25°. The conjugation between the rings would also be expected to tend to diminish the angle between the rings, but, as they can obviously approach much nearer to coplanarity when the groups are *trans* to one another, conjugation would be expected to favour the latter disposition Again, the effect of London forces, such as was suggested by Hampson and Weissberger, might be expected to cause the groups to reside in the *cis*- rather longer than in the corresponding *trans*-configuration. On such a theory, however, the mean value of ϕ would be expected to increase much more than is observed on passing from the fluoro- to the iodo-compound.

Table 2 also includes similar interpretations of the dipole moment of 3 : 3′-dinitrodiphenyl now recorded and of the moment for 3 : 3′-dichlorodiphenyl reported by Hampson and Weissberger. The particular point of interest here is that the mean angle of inclination of the rings is slightly above 90°, *i.e.*, there is a slight tendency in each case for the groups to have a preferential *trans*-disposition, but the actual inter-planar angle is of the same order as in the 2 : 2′-derivatives, *viz.*, 75° and 83° for 3 : 3′-dinitro- and 3 : 3′-dichloro-diphenyl, respectively. From electron-diffraction measurements, Bastiansen (*Acta Chem. Scand.*, 1949, **3**, 408) deduced that the angle between the planes of the rings was 54° ± 5° in 3 : 3′-dibromodiphenyl and 52° ± 10° in 3 : 3′-dichlorobenzidine, compared with 45° ± 10° for diphenyl itself. The halogen atoms appear to have a *trans*-disposition in each case. On the other hand *X*-ray crystal analysis of 3 : 3′-dichlorobenzidine indicates that in the solid state this molecule is probably planar or very nearly so, with the chlorine atoms *trans* to one another (Toussaint, *Acta Cryst.*, 1948, **1**, 43).

Experimental

Preparation and Purification of Materials.—2 : 2′-Dinitrodiphenyl, prepared by Shaw and Turner's method (*J.*, 1933, 135) and recrystallised from light petroleum (b. p. 100—120°), had m. p. 125·5° (lit., 123·5—124·5°).

Table 3.

100*w*	ε	*v*	*n*	100*w*	ε	*v*	*n*
	2 : 2′-Difluorodiphenyl				2 : 2′-Di-iododiphenyl		
0·0000	2·2725	1·14454	1·4981	0·0000	2·2725	1·14462	1·4980
0·8103	2·2898	1·14192	1·4984	1·1007	2·2834	1·13732	—
1·4294	2·3030	1·13994	1·4987	1·7043	2·2897	1·13333	1·4993
2·3099	2·3217	1·13726	1·4990	2·2749	2·2952	1·12951	1·4997
2·7155	2·3344	1·13548	1·4993	2·6877	2·2998	1·12677	1·5001
4·1031	2·3610	1·13162	1·4999	3·3174	2·3061	1·12263	1·5006
				3·7024	2·3096	1·12007	1·5009
	2 : 2′-Dichlorodiphenyl				2 : 2′-Dinitrodiphenyl		
0·0000	2·2725	1·14462	1·4980				
0·8710	2·2913	1·14150	1·4986	0·0000	2·2725	1·14459	1·4981
1·3960	2·3020	1·13955	1·4991	0·2506	2·3022	1·14349	1·4983
2·1093	2·3172	1·13708	1·4996	0·3720	2·3169	1·14294	1·4984
2·3441	2·3221	1·13622	1·4998	0·6009	2·3448	1·14201	1·4986
2·6680	2·3290	1·13507	1·5001	0·7729	2·3655	1·14129	1·4987
3·2365	2·3412	1·13302	1·5005	0·9357	2·3861	1·14054	1·4989
				1·3687	2·4399	1·13876	1·4992
	2 : 2′-Dibromodiphenyl				3 : 3′-Dinitrodiphenyl		
0·0000	2·2725	1·14462	1·4980				
1·0275	2·2874	1·13884	1·4988	0·0000	2·2725	1·14460	1·4979
1·6191	2·2926	1·13554	1·4989	0·1099	2·2809	1·14412	1·4980
2·3093	2·3065	1·13164	1·4997	0·4168	2·3058	1·14277	1·4982
2·9714	2·3160	1·12794	1·5002	0·8921	2·3435	1·14072	1·4985
3·9714	2·3311	1·12233	1·5009	1·3256	2·3783	1·13877	1·4989
4·6202	2·3409	1·11867	1·5014	1·4978	2·3925	1·13801	1·4991

2 : 2′-Diaminodiphenyl was prepared by reducing 2 : 2′-dinitrodiphenyl with iron filings and water in the presence of a little acetic acid, the product being made alkaline with ammonia and extracted with acetone. The acetone was distilled off, the residue extracted with hydrochloric acid, and the extract made alkaline with ammonia. The precipitated amine was separated and extracted with light petroleum (b. p. 40—60°) in a Soxhlet apparatus. The product separating from the extract had m. p. 81° (lit., 78—81°).

2 : 2′-Difluorodiphenyl, prepared from 2 : 2′-diaminodiphenyl by Schiemann and Roselius's method (*Ber.*, 1932, **65**, 737) and recrystallised from alcohol, had m. p. 118·5° (lit., 117—117·5°).

2 : 2′-Dichlorodiphenyl, prepared from 2 : 2′-dinitrodiphenyl by Mascarelli and Gatti's method (*Gazzetta*, 1932, **59**, 868) and recrystallised from methyl alcohol, had m. p. 61·5° (lit., 59—62°).

2 : 2′-Dibromodiphenyl, prepared from 2 : 2′-diaminodiphenyl by Schwechten's method (*Ber.*, 1932, **65**, 1605) and recrystallised from methyl alcohol, had m. p. 81·5° (lit., 80—81°).

2 : 2′-Di-iododiphenyl, prepared from 2 : 2′-diaminodiphenyl by Lothrop's method (*J. Amer. Chem. Soc.*, 1941, **63**, 1187) and recrystallised from ethyl alcohol, had m. p. 110° (lit., 108°).

3 : 3′-Dinitrodiphenyl, lent by Professor E. E. Turner and recrystallised from ethyl alcohol, had m. p. 199° (lit., 197—200°).

Apparatus and Measurements.—The dielectric constants, specific volumes, and refractive indices of the solutions at 25·0° are recorded in Table 3. These were determined by the methods used in Part II, and the parameters listed in Table 1 were derived from these figures by the same devices as previously.

The authors are indebted to Professor E. E. Turner, F.R.S., Dr. D. M. Hall, and Dr. G. H. Beaven for valuable discussions. Thanks are also due to the Department of Scientific and Industrial Research for a Maintenance Grant (to A. C. L.), and to Imperial Chemical Industries Limited for the loan of a precision variable condenser.

BEDFORD COLLEGE, REGENT'S PARK, LONDON, N.W.1. [*Received, March 1st*, 1954.]

Mesomorphism and Chemical Constitution. Part III. The Effect of Halogen Substitution on the Mesomorphism of the 4-Alkoxybenzoic Acids.*

By G. W. GRAY and BRYNMOR JONES.

[Reprint Order No. 5187.]

The preparation and mesomorphic character of certain 4-*n*-alkoxy-3-halogenobenzoic acids are described. Halogen-substitution results in an increase in the breadth of the molecule which is reflected in the relative thermal stabilities of the mesophases. With fluorine and chlorine the increase is not sufficient to eliminate the mesomorphism, but the thermal stabilities of the phases of the broader chloro-acids are lower than those for the corresponding fluoro-acids. The presence of one bromine atom, or two chlorine atoms, as in 4-*n*-alkoxy-3 : 5-dichlorobenzoic acids, is sufficient to destroy the mesomorphism of the unsubstituted acids.

IT is generally recognised that, apart from such molecules as the esters of cholesterol, long rod-shaped molecules are the most likely to exhibit mesomorphism. This is true only if the intermolecular cohesion is sufficient to maintain the linear molecular arrangement in the mesophase at elevated temperatures. When the breadth of a mesomorphic compound is increased by substitution the intermolecular cohesion may be lowered, as a result of the increased separation of the molecules from one another. The melting points and the mesomorphic transition temperatures (smectic–nematic, and smectic– or nematic–isotropic) should then be lower in the substituted than in the unsubstituted compounds.

Such behaviour has been found for 4-*n*-alkoxy-3-fluoro-, -3-chloro-, and -3-bromobenzoic acids, whose physical constants are tabulated below. Figures in parentheses

* Part II, *J.*, 1954, 1467.

relate to monotropic transitions, or to the lengths of monotropic phases. The usual thirteen ethers (methyl—decyl, dodecyl, hexadecyl, and octadecyl) used in these studies were not prepared, since the lower members show no mesomorphism.

4-Alkoxy-3-fluorobenzoic acids.

Alkyl group	Temp. of transition to smectic	nematic	isotropic	Phase length of smectic	nematic
Methyl	—	—	211·5°	—	—
Butyl	—	—	143·5	—	—
Pentyl	—	—	137·5	—	—
Hexyl	—	—	129·5	—	—
Heptyl	—	—	124	—	—
Octyl	—	117°	120·5	—	3·5°
Nonyl	(<110°) *	112	116·5	(>2°)	4·5
Decyl	108	112	116·5	4	4·5
Dodecyl	108·5	113	114·5	4·5	1·5
Hexadecyl	94	—	111	17	—
Octadecyl	(109)	—	114	(5)	—

* Possible extrapolated value 109°.

3-Fluoro-4-nonyloxybenzoic acid exhibits a monotropic smectic phase, which is seen only if the nematic melt is cooled rapidly. It was impossible to determine this transition, since the slow cooling which is necessary to obtain accurate monotropic transitions resulted in crystallisation at 110°. A value only one degree lower than this is however indicated for the transition from the gradient of the curve (Fig. 1) through the smectic–nematic and smectic–isotropic transitions of the higher ethers. In this series the m. p. rises steeply to the octadecyl ether, whereafter the smectic phase again becomes monotropic. In this case, the isotropic liquid may be cooled without inducing crystallisation, and the reversal to the mesophase was obtained at 109°. A smooth curve (Fig. 1) may be drawn through

FIG. 1. *4-Alkoxy-3-fluorobenzoic acids.*

● *Solid–mesophase or isotropic liquid.*
⊗ *Smectic–nematic.*
○ *Nematic–isotropic.*
⊕ *Smectic–isotropic.*

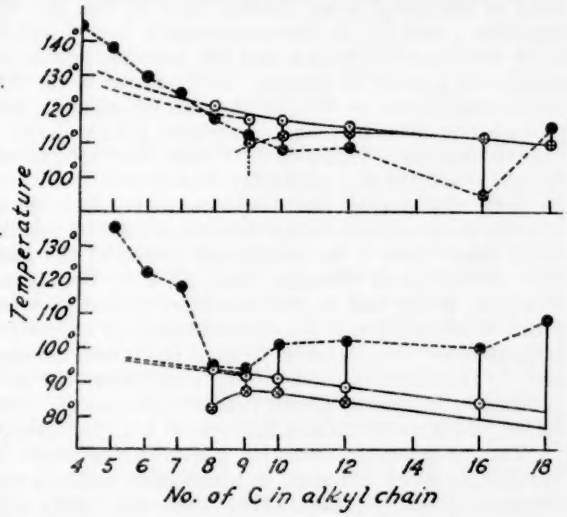


FIG. 2. *4-Alkoxy-3-chlorobenzoic acids.*

the smectic– and nematic–isotropic transition points for the acids which have an even number of carbon atoms in the alkyl chain. As is to be expected, the upper transition point of the nonyl ether lies below this curve, because of the usual alternations found in homologues containing odd and even numbers of carbon atoms in the alkyl chain. The curve for the even members has been extrapolated in the direction of the shorter alkyl groups, and an equivalent curve drawn from the upper transition point of the nonyl ether (broken curves in Fig. 1). The heptyl, hexyl, and pentyl ethers are not mesomorphic, but these curves indicate that their upper transition points would be 121°, 126°, and 126·5° respectively. These temperatures are very close to the observed m. p.s for these ethers.

Their melts show very little tendency to supercool, however, and crystallise within 1—3° of their m. p.s, so that the phases, which would be monotropic, are not observed. A curve may be drawn through the smectic–nematic points of the decyl and dodecyl ethers and the smectic–isotropic points of the last two ethers in the series. The latter are purely smectic, and appear from the isotropic liquid in bâtonnets.

4-Alkoxy-3-chlorobenzoic acids.

Alkyl group	Temp. of transition to smectic	Temp. of transition to nematic	Temp. of transition to isotropic	Phase length of smectic	Phase length of nematic
Methyl	—	—	217·5°	—	—
Pentyl	—	—	134·5	—	—
Hexyl	—	—	121	—	—
Heptyl	—	—	117	—	—
Octyl	(81·5°)	(93°)	94	(11·5°)	(1°)
Nonyl	(86·5)	(91)	93·5	(4·5)	(2·5)
Decyl	(86)	(90·5)	100·5	(4·5)	(10)
Dodecyl	(83·5)	(88)	101·5	(4·5)	(13·5)
Hexadecyl	(78·5) *	(83)	99·5	(4·5)	(16·5)
Octadecyl	(76·5) *	(81) *	107·5	(4·5)	(26·5)

* Extrapolated values.

In the chloro-acids all the mesophases are monotropic, appearing only from the supercooled melts. At the octyl ether, which, like the higher ethers, exhibits both a smectic and a nematic phase, there is a considerable fall in m. p. The transitions for isotropic–nematic (cooling) or nematic–isotropic (heating from the supercooled state) for the octyl to hexadecyl ethers lie on a straight line. The analogous point for the nonyl ether is slightly lower, because of odd–even alternation. As in the fluoro-series, this line has been extrapolated, and another line drawn parallel to it from the nematic–isotropic transition point of the nonyl ether (broken lines in Fig. 2). These lines give the hypothetical transition points for the non-mesomorphic heptyl and hexyl ethers. The values lie well below the observed m. p.s, and the isotropic liquids cannot be supercooled sufficiently rapidly for a phase to appear. Continuation of the straight line to octadecyl yields an extrapolated value, at 81°, for the isotropic–nematic transition. A curve may be drawn through the smectic–nematic transition points of the octyl to dodecyl ethers, and its continuation gives values of 78·5° and 76·5° for the smectic–nematic transitions of the hexadecyl and the octadecyl ether respectively.

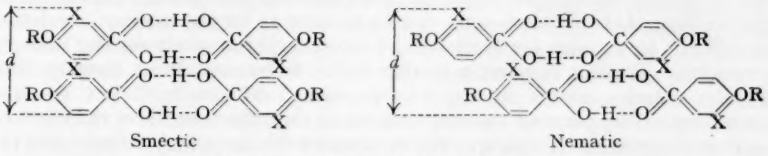
In the chloro-series, nematic properties persist in the hexadecyl and the octadecyl ether, whereas in other homologous series molecules of this length are purely smectic. In the latter cases, there is no preliminary sliding of the molecules to an imbricated nematic state (Friedel, *Ann. Physique*, 1922, **17**, 273; Bernal and Crowfoot, *Trans. Faraday Soc.*, 1933, **29**, 1016), and at the mesomorphic–isotropic transition the lateral, planar, and terminal cohesions must loosen simultaneously to give the disordered isotropic state. The large chlorine atom must so weaken the lateral cohesion that the molecules are able to slide in the direction of their long axes, before the cohesion between terminal groups is sufficiently reduced to permit random orientation. The sliding would produce a nematic phase, which would become isotropic at a higher temperature.

The mesomorphic transition points in the fluoro- and the chloro-series exhibit the regularities which are usual in homologous series of mesomorphic compounds (Gray and Brynmor Jones, *J.*, 1953, 4179; 1954, 683, 1467). The 4-alkoxy-3-bromobenzoic acids are not mesomorphic, and melts of the octyl ether (m. p. 111°) and hexadecyl ether (m. p. 99°) could be cooled to 90° and 81° respectively, before crystallising. If therefore these compounds were mesomorphic, their mesophases would appear below these temperatures and would be less stable than the mesophases of the analogous chloro-compounds.

In an earlier preliminary account of the behaviour of the 4-alkoxy-3-fluoro- and -3-chloro-benzoic acids (Gray and Brynmor Jones, *Nature*, 1952, **170**, 451) the phase lengths were derived from transition temperatures determined in a capillary tube: the present determinations were made in an electrically heated microscope block (Gray, *Nature*, 1953,

172, 1137), in which control was more accurate. The results for the 3-fluoro-series were virtually the same, but the 3-chloro-acids soften to some extent before melting, and, in a capillary tube, the impression is created of short enantiotropic phases. When the m. p. is determined on a thin section of solid observed under a microscope, the effect is only one of slight lattice deterioration, which is most marked in the longer-chain homologues. The phases of the chloro-acids are therefore monotropic.

The acids are believed to exist in the mesophases as dimers in their state of lowest potential energy, with the 3-substituents *trans* to one another. The packing of the molecules in the mesophases will however be determined by the breadth of the monomer, and not by the overall breadth of the dimer. This is obvious when two molecules are arranged side by side, in such a way as to give potential smectic and nematic orientations (Friedel; Bernal and Crowfoot, *locc. cit.*).



(*d* is twice the breadth of the monomer)

The breadths of the monomers were obtained by calculation, 1·2 Å being taken as the van der Waals radius of hydrogen. As the breadths increase progressively in the order *p*-*n*-alkoxy-, 4-*n*-alkoxy-3-fluoro-, 4-*n*-alkoxy-3-chloro-benzoic acids there is a decrease in the mesomorphic–isotropic transition temperatures, and consequently in mesomorphic stability. Only the nematic–isotropic transitions for the octyl–hexadecyl ethers can be obtained in all three series without extrapolation, and these alone are considered in the following Table.

X = 3-substituent	H		F		Cl
Average transition (mesomorphic–isotropic for C_8 to C_{16})	140·3°		115·8°		89·1°
Decrease in average transition		24·5°		26·7°	
Increase in molecule breadth (Å)		0·43		0·75	

In comparing the change from unsubstituted to fluoro-acid and from unsubstituted to chloro-acid, two opposing effects must be considered in each case. These are the increase in breadth, which should decrease the mesomorphic stability, and the introduction of the carbon–halogen dipole, which should increase the mesomorphic stability. The C–F and C–Cl dipoles being taken as 1·57 and 1·73 μ * respectively, the decrease in average transition temperature/Å from unsubstituted to fluoro-acid should be greater than that from unsubstituted acid to chloro-acid. This is shown qualitatively by calculating the ratios of the decrease in average transition to the breadth increases. These ratios are the fall in average transition temperature/Å, and are 56·98 from unsubstituted to fluoro-acid, and 43·39 from unsubstituted to chloro-acid, in agreement with the order predicted above.

The smectic–nematic transition temperatures also decrease with increasing molecular breadth, and the average values for the decyl and the dodecyl ethers have been considered similarly to the mesomorphic–isotropic transitions.

X = 3-substituent	H		F		Cl
Average smectic–nematic transition (C_{10} and C_{12}) ...	125·5°		112·5°		84·75°
Decrease in average transition		13°		27·75°	
Increase in molecule breadth (Å)		0·43		0·75	

The ratios are now 30·23 from unsubstituted to fluoro-acid, and 34·53 from unsubstituted to chloro-acid. The order is reversed from that for the mesomorphic–isotropic transitions, and is in disagreement with the order of the effective dipole moments.

In neither case has it been possible to find a mathematical relation which will give values for the relative effects of the dipoles and the breadth increases in accordance with the

* Dipole moments from H. B. Watson's "Modern Theories of Organic Chemistry," 2nd Edn., Oxford Univ. Press, London, 1941, 60.

observed transitions. These results can only indicate qualitatively that relatively small increments in molecular breadth do decrease the thermal stability of the mesophases. Before it is possible to suggest even an approximate mathematical treatment for the effect of substitution on mesomorphic systems, further data will have to be obtained by an examination of other substituted homologous series.

It must be assumed that the 4-alkoxy-3-bromobenzoic acids are too broad to be mesomorphic, as a result of their weaker intermolecular cohesion. The 4-alkoxy-3 : 5-dichlorobenzoic acids (breadth increment from unsubstituted acid = 1·5 Å) are not mesomorphic, and the low m. p.s of the pentyl and the hexadecyl ethers, 103° and 60·5° respectively, imply a still lower intermolecular cohesion in the crystal. Indeed, any molecular arrangement which would give smectic behaviour would be much more open than that for the 3-chloro-acids, and the cohesion would be still further reduced by opposition of the carbon–halogen dipoles between different molecules. On the other hand, a nematic packing of the dichloro-acids can be as close as for the monochloro-derivatives, and it is difficult to account for their lack of mesomorphism solely on the basis of their greater breadth. There is however a further factor to be considered, namely, the steric effect of the chlorine atoms in the 3 : 5-positions. This is sufficient to force the O–CH_2 bond out of the plane of the ring system, so that the breadth of the alkyl chain is at an angle to this plane. In this way the monomer's thickness may be increased to about 4·8 Å, compared to the thickness of 3·7 Å for the unsubstituted, 3-fluoro-, and 3-chloro-acids. The result will be a reduction in the cohesion between the planes of the aromatic rings, sufficient to give a low crystal lattice energy, and presumably to make mesophases impossible by rendering them stable only at temperatures which are too low to be obtained without crystallisation. The breadth of the dichloro-acid molecules is probably of little significance compared to the effect of this thickening of the molecule.

Experimental

(M. p.s are corrected for exposed stem.)

The mesomorphic and polymorphic transitions were determined in an electrically heated block (Gray, *loc. cit.*). The enantiotropic mesomorphic changes were measured in the usual way : all the values except those from the solid to the mesophase were checked both by heating and by cooling the specimen. The changes observed in polarised light were from the solid to the fine mosaic of smectic focal-conics, from the solid or smectic phase to the highly threaded, mobile nematic phase, and from the solid or mesophase to the extinct isotropic liquid. The monotropic mesomorphic transitions were determined by observing carefully the isotropic liquid as it cooled slowly until the nematic phase and, at a lower temperature, the smectic phase appeared. It was sometimes possible to raise the temperature while the specimens were in these monotropic states without inducing crystallisation, and thus to obtain the transitions in reverse. Good agreement was found with the values obtained on cooling. Frequently the low rate of cooling (about 1° per min.), which was necessary for accurate measurement of the transitions, was too slow, and crystallisation occurred. In these cases, values of the transition temperatures could be obtained only by extrapolation of the curves constructed from experimentally observed values for the other members of the series.

Polymorphic Transition Temperatures.—See Tables. Here solid I is the stable solid at room temperature.

4-n-*Alkoxy*-3-*fluorobenzoic acids.*

Alkyl	Solid I–solid II transition temp.
Butyl	137·5°
Pentyl	99·5
Hexyl	74·0
Heptyl	101·5
Octyl	94·0
Nonyl	109·0
Decyl	106·0
Octadecyl	75·5

The dodecyl ether exhibits two monotropic forms.

4-n-*Alkoxy*-3-*chlorobenzoic acids.*

Alkyl	Solid I–solid II transition temp.
Heptyl	111·0°
Octyl	90·0
Nonyl	85·0

Both the decyl and the dodecyl ethers exhibit a monotropic solid.

Preparation of Materials.—*o*-Fluoroanisole was obtained from *o*-anisidine in 40% yield by decomposition of the dry diazonium borofluoride (Balz and Schiemann, *Ber.*, 1927, **60**, 1186). It was purified by fractionation and had b. p. 160—162°.

4-*Bromo*-2-*fluoroanisole*.—The *o*-fluoroanisole (18·9 g., 0·15 mole) was treated in chloroform (50 ml.) gradually with bromine (24 g., 0·15 mole) at room temperature. When the initial reaction had subsided, the mixture was refluxed gently until bromination was complete (2·5 hr.). The cooled solution was washed with water and with dilute sodium hydroxide and dried. After the solvent had been recovered, and pale yellow oil distilled under reduced pressure, 4-*bromo*-2-*fluoroanisole* was obtained as a colourless liquid, b. p. 148—150°/14 mm., in 95% yield (Found : C, 41·0; H, 3·0; Br, 38·9. C_7H_6OBrF requires C, 41·0; H, 2·9; Br, 39·0%).

3-*Fluoro*-4-*methoxybenzoic Acid*.—The Grignard compound from 4-bromo-2-fluoroanisole was prepared in anhydrous ether–benzene and converted into the acid by the method described by Fries and Schimmelschmidt (*Ber.*, 1925, **58**, 2835) for 6-methoxy-2-naphthoic acid. After carboxylation and acidification, and removal of most of the ether, the crude acid was collected and freed from neutral matter by dissolution in hot dilute sodium hydroxide. The product obtained on acidification (28·5 g., 67%) had m. p. 211·5°, unchanged by crystallisation from glacial acetic acid and ethyl alcohol. The *acid* crystallised as colourless prisms (Found : C, 56·4; H, 4·1. $C_8H_7O_3F$ requires C, 56·5; H, 4·1%). The benzene layer in the filtrate from the crude acid gave only a small amount of impure acid on extraction with aqueous alkali.

3-*Fluoro*-4-*hydroxybenzoic Acid*.—3-Fluoro-4-methoxybenzoic acid (45 g.) was demethylated by refluxing 48% hydrobromic acid (100 ml.) and glacial acetic acid (100 ml.) for 6—7 hr. More than half of the hydroxy-acid (m. p. 148—157°) was obtained crystalline on cooling; the remainder, of the same m. p., was isolated by removal of the solvent under reduced pressure. Crystallisation from water, and filtration of the hot solution to remove some insoluble material, yielded colourless needles, m. p. 145—147° (36 g., 87%). Further crystallisation from 30% acetic acid raised the m. p. to 146—147° (Found : C, 53·0; H, 3·8. Calc. for $C_7H_5O_3F$: C, 53·9; H, 3·2%). Attempts at further purification failed to improve the m. p. and the analysis. The ethers of this hydroxy-acid were very readily purified, and the use of the impure material was not a handicap.

4-n-*Alkoxy*-3-*fluorobenzoic Acids*.—3-Fluoro-4-hydroxybenzoic acid (1·56 g., 0·01 mole), potassium hydroxide (1·1 g., 0·02 mole), water (5 ml.), ethyl alcohol (40 ml.), and the *n*-alkyl halide (0·015 mole) were refluxed (alkyl iodide 8 hr.; alkyl bromide 16 hr.). Aqueous potassium hydroxide (10 ml., 10%) was added, and refluxing continued for 2 hr. to hydrolyse any ester. The pure *alkoxy-acids* were obtained as colourless needles or prisms after one crystallisation from absolute alcohol, two from benzene, and one from glacial acetic acid. After the first crystallisation the acids were almost pure : the yields at this stage were 80—85%.

4-n-*Alkoxy*-3-*fluorobenzoic acids*.

	Found (%)			Required (%)			Found (%)			Required (%)	
Alkyl	C	H	Formula	C	H	Alkyl	C	H	Formula	C	H
Butyl ...	62·4	6·3	$C_{11}H_{13}O_3F$	62·3	6·1	Nonyl ...	68·2	8·3	$C_{16}H_{23}O_3F$	68·1	8·2
Pentyl	63·7	6·7	$C_{12}H_{15}O_3F$	63·7	6·6	Decyl.....	69·1	8·5	$C_{17}H_{25}O_3F$	68·9	8·5
Hexyl...	65·2	7·1	$C_{13}H_{17}O_3F$	65·0	7·1	Dodecyl...	70·6	8·8	$C_{19}H_{29}O_3F$	70·4	9·0
Heptyl	66·2	7·4	$C_{14}H_{19}O_3F$	66·2	7·5	Hexadecyl	72·5	9·8	$C_{23}H_{37}O_3F$	72·6	9·7
Octyl ...	67·3	7·8	$C_{15}H_{21}O_3F$	67·2	7·8	Octadecyl	73·4	9·9	$C_{25}H_{41}O_3F$	73·5	10·1

3-*Chloro*-4-*hydroxybenzoic Acid*.—*p*-Hydroxybenzoic acid (13·8 g., 0·1 mole) was treated in acetic acid (100 ml.) with a solution of dichloramine-T (12 g., 0·05 mole) in acetic acid (100 ml.) and concentrated hydrochloric acid (0·5 ml.). After 2 hr. the acetic acid (100 ml.) was removed under reduced pressure. The cooled liquors deposited colourless crystals, m. p. 169—172° (14 g.). One crystallisation from water gave 3-chloro-4-hydroxybenzoic acid, m. p. 172° (12·3 g., 70%).

4-n-*Alkoxy*-3-*chlorobenzoic Acids*.—3-Chloro-4-hydroxybenzoic acid was alkylated in the same way as 3-fluoro-4-hydroxybenzoic acid. After one crystallisation from glacial acetic acid the *ethers* were obtained as colourless needles or prisms in yields of 85—95%. These were purified by crystallisation from benzene (twice) and from absolute alcohol (twice).

3-*Bromo*-4-*hydroxybenzoic Acid*.—*p*-Hydroxybenzoic acid was brominated in acetic acid with the theoretical amount of bromine. The acid precipitated on dilution with water was washed and dissolved in aqueous sodium hydrogen carbonate. The solution was filtered, and the acid liberated. Crystallisation from water gave colourless needles of the bromo-acid, m. p. 177·5° (80%).

4-n-*Alkoxy*-3-*chlorobenzoic acids.*

Alkyl	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl
Methyl *	51·5	3·8	19·1	$C_8H_7O_3Cl$	51·5	3·8	19·0
Pentyl *	59·6	6·3	14·6	$C_{12}H_{15}O_3Cl$	59·4	6·2	14·7
Hexyl	60·7	6·6	13·9	$C_{13}H_{17}O_3Cl$	60·8	6·6	13·8
Heptyl	62·2	7·2	13·1	$C_{14}H_{19}O_3Cl$	62·1	7·0	13·1
Octyl	63·3	7·5	12·5	$C_{15}H_{21}O_3Cl$	63·3	7·4	12·5
Nonyl	64·4	7·7	12·0	$C_{16}H_{23}O_3Cl$	64·3	7·7	11·9
Decyl	65·3	7·8	11·5	$C_{17}H_{25}O_3Cl$	65·3	8·0	11·4
Dodecyl	66·9	8·5	10·4	$C_{19}H_{29}O_3Cl$	66·95	8·5	10·4
Hexadecyl	69·6	9·5	8·9	$C_{23}H_{37}O_3Cl$	69·6	9·3	8·95
Octadecyl	70·7	9·7	8·4	$C_{25}H_{41}O_3Cl$	70·7	9·7	8·4

* Not new.

4-n-*Alkoxy*-3-*bromobenzoic Acids.*—Only the octyl and hexadecyl ethers were prepared, and these were almost pure after one crystallisation from glacial acetic acid (the yields at this stage were 85%). Both were crystallised thrice from glacial acetic acid and once from benzene to give colourless plates of the *octyl ether*, m. p. 111° (Found: C, 55·0; H, 6·5; Br, 24·4. $C_{15}H_{21}O_3Br$ requires C, 54·8; H, 6·4; Br, 24·3%), and the *hexadecyl ether*, m. p. 99° (Found: C, 62·6; H, 8·4; Br, 18·2. $C_{23}H_{37}O_3Br$ requires C, 62·6; H, 8·4; Br, 18·1%).

3 : 5-*Dichloro*-4-*hydroxybenzoic Acid.*—Chlorine was passed through a solution of *p*-hydroxybenzoic acid in glacial acetic acid for 4 hr. at 60—80°. The resulting thick suspension was cooled and the solid collected. It was stirred with aqueous sodium dithionite, refiltered, washed with water, and dried. The product (76%) was nearly pure, and had m. p. 265—267°. Crystallisation from a large volume of glacial acetic acid gave colourless needles of the dichloro-acid, m. p. 267°. Ugryumov (*J. Gen. Chem. U.S.S.R.*, 1949, **19**, 1167) gives m. p. 265°.

4-n-*Alkoxy*-3 : 5-*dichlorobenzoic Acids.*—The *pentyl* and *hexadecyl ethers* were prepared. The crude ethers contained some unchanged hydroxy-acid, and for 0·01 mole of the ethers this was removed by shaking with 30 and 70 ml. of cold benzene in the cases of the pentyl and hexadecyl ethers respectively. The solutions were filtered and evaporated to yield the colourless ethers, which were then purified by further crystallisation. The pentyl ether, crystallised from glacial acetic acid and light petroleum ether (b. p. 60—80°), had m. p. 103° (Found: C, 51·8; H, 5·1; Cl, 25·6. $C_{12}H_{14}O_3Cl_2$ requires C, 52·0; H, 5·1; Cl, 25·6%). The hexadecyl ether, crystallised twice from light petroleum (b. p. 40—60°), melted at 60·5° (Found: C, 64·1; H, 8·3; Cl, 16·5. $C_{23}H_{36}O_3Cl_2$ requires C, 64·0; H, 8·3; Cl, 16·5%).

Grants to the Department from the Distillers Company Limited and from Imperial Chemical Industries Limited are gratefully acknowledged.

UNIVERSITY COLLEGE, HULL. [*Received, March 6th*, 1954.]

Studies on Xanthorrhoea *Resins. Part I. Isolation of Chrysophanic Acid* (1 : 8-*Dihydroxy*-3-*methylanthraquinone*) *and of* 2′ : 4-*Dihydroxy*-4′-*methoxychalkone.*

By HEINZ DUEWELL.

[Reprint Order No. 5193.]

The isolation of chrysophanic acid from bushfire-damaged *Xanthorrhoea* resin, in which it is found as an artifact, is described. 2′ : 4-Dihydroxy-4′-methoxychalkone has been isolated from *X. australis* resin.

THE object of the present work is to study the colouring matters of *Xanthorrhoea* resins and possibly throw some light on the nature of the resin itself. Earlier investigations summarized by Tschirch and Stock ("Die Harze," Borntraeger, Berlin, 1935, Vol. II, 135) do not concern themselves with these aspects. Resins from three *Xanthorrhoea* species were examined in a preliminary manner. The first, from an unidentified species growing in the National Park, Sydney, N.S.W., was used for early fractionations. Subsequently resins from *X. resinosa*, Pers. (Peat's Ferry, N.S.W., and Melbourne Botanical Gardens) and from *X. australis*, R.Br. (Mangalore, Vic., Gembrook, Vic., and the Grampians, Vic.) were studied.

After removal of alcohol-insoluble material the resin of unknown origin was largely precipitated from its solution in benzene by the addition of light petroleum. From the material still in solution orange crystals of chrysophanic acid were isolated. Paper chromatograms of the resins of *X. resinosa* (Botanical Gardens) and *X. australis* were simpler than that of the unidentified resin, and it was not possible to show the presence of chrysophanic acid, even after the removal of the bulk of the resin body. As the protruding part of the leaf bases of the unidentified resin had been charred by a bushfire, it appeared likely that chrysophanic acid would only be found in such resin. This was confirmed, for slightly burnt resin samples from both *X. resinosa* and *X. australis* afforded chrysophanic acid. It was also produced by igniting a fresh piece of *X. australis* resin.

As yet no survey of the resins from different *X.* species has been made, but from a comparison of paper chromatograms of resins from *X. resinosa* and *X. australis* it appears likely that some pigments may be species-specific. 2′ : 4-Dihydroxy-4′-methoxychalkone which has now been isolated from *X. australis* may be such a compound, for it could not be found in resins from *X. resinosa*. This appears to be the first time that this chalkone has been isolated from a natural source.

One of the volatile products of prolonged steam-distillation of a strongly alkaline solution of the resins of *X. tateana*, *X. Preissii* (Rennie, Cooke, and Finlayson, *J.*, 1920, **117**, 338), *X. resinosa*, *X. hastilis*, and *X. reflexa* (Finlayson, *J.*, 1926, 2763) is paeonol (2-hydroxy-4-methoxyacetophenone) and it may arise, in part at least, from the decomposition of 2′ : 4-dihydroxy-4′-methoxychalkone, which was shown to produce paeonol under these conditions.

Experimental

X. sp. *Resin from National Park, Sydney, N.S.W.—Purification.* After removal of plant debris by dissolution of the resin in ethanol and filtration, the completely alcohol-free resin (83 g.) was extracted with hot benzene (8 × 250 ml.), and the yellow extract removed by decantation. After some resinous matter had been allowed to settle, the solution was again decanted and left a brittle, somwehat sticky, orange-red resin after evaporation.

Fractional precipitation and isolation of chrysophanic acid. The benzene-soluble portion (17 g.) from the purified resin was dissolved in benzene (200 ml.), and light petroleum (b. p. 40—60°; 200 ml.) was added. The precipitate was removed and the filtrate evaporated to dryness. The residue was dissolved in benzene (25 ml.), and light petroleum (100 ml.) added, giving a further precipitate and material in solution. Evaporation of this solution left an oil to which ethanol was added. Crude chrysophanic acid crystallised and was filtered off warm to prevent the precipitation of a white contaminant. The product (15 mg.) had m. p. and mixed m. p. 193·5° (from ethanol) (Found: C, 70·6; H, 4·1; OMe, 0·0. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 4·0%). The diacetate had m. p. and mixed m. p. 207·5—208° (Found: C, 67·6; H, 4·4. Calc. for $C_{19}H_{14}O_6$: C, 67·5; H, 4·2%). The ultra-violet spectrum of chrysophanic acid was in agreement with that of a 1 : 8-dihydroxyanthraquinone (Morton and Earlem, *J.*, 1941, 159), *viz.*: in EtOH, max. at 224, 257, 277, 287, and 430 mμ (log ε 4·54, 4·30, 3·99, 4·03, and 4·01, respectively); in EtOH containing NaOEt, max. at 285, 365—380, and 504 mμ (log ε 3·92, 3·28, and 3·94, respectively).

Resins from X. resinosa *and* X. australis.—*Isolation of chrysophanic acid from charred* X. resinosa *resin.* The resin (190 g., freed from plant material by extraction with ethanol) was worked up as described above. The ether extract of crude chrysophanic acid was extracted with 2N-sodium carbonate and finally with N-sodium hydroxide. Acidification of the sodium hydroxide extract gave chrysophanic acid (75 mg.), melting at 188—189° (from ethanol). Sublimation (125—130°) at 10^{-4} mm. gave material with m. p. and mixed m. p. 194—194·5° (from ethanol). The diacetate after sublimation (150—160°/10^{-4} mm.) had m. p. and mixed m. p. 208·5—209° (from benzene).

Chrysophanic acid produced by burning X. australis *resin.* A large piece of *X. australis* resin was ignited at one end, the charred portion extracted with ethanol, the ethanol removed, and the residue treated with hot benzene. The solution was decanted and extracted successively with solutions of sodium hydrogen carbonate, sodium carbonate, and sodium hydroxide. The sodium hydroxide extract was red and the precipitate formed on acidification when examined in a circular paper chromatogram (Whatman No. 1 and benzene) showed chrysophanic acid at the solvent front by its red colour in ammonia vapour. The unburnt portion of the resin did not show chrysophanic acid when treated similarly.

Isolation of 2′ : 4-*dihydroxy*-4′-*methoxychalkone from* X. australis *resin.* The resin (20 g.) was dissolved in ethanol (250 ml.), partly precipitated by the addition of water (250 ml.), and filtered with the help of Filter-Cel (40 g.). The benzene extract of the filtrate was then shaken successively with saturated aqueous sodium hydrogen carbonate (3 × 100 ml.), 2N-sodium carbonate (8 × 50 ml.), and N-sodium hydroxide (3 × 100 ml.). With sodium carbonate complete extraction was impossible. The extracts were acidified (10N-sulphuric acid) and left overnight to allow the precipitate to coagulate. The material extracted by sodium hydroxide was granular and removed by filtration (0·66 g.). A benzene-insoluble amorphous impurity was removed. The crude pigment melted at 166—167° (0·33 g. of yellow needles from aqueous ethanol). The crystals were redissolved in benzene by warming and the solution repeatedly extracted with 2N-sodium carbonate (7 × 100 ml.) in which the chalkone formed a deep yellow solution. Acidification gave a product (0·29 g.) melting unchanged at 172° (0·25 g. from aqueous ethanol) (Found: C, 71·2; H, 5·0; OMe, 11·7. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2; OMe, 11·5%). A synthetic specimen prepared according to the directions of Geissman and Clinton (*J. Amer. Chem. Soc.*, 1946, **68**, 697) melted at 172° and showed no depression when admixed with the natural product. The ultra-violet absorption spectra of the two materials were identical, with maxima (in EtOH) at 240 and 371 mμ and a point of inflection at 309 mμ (log $\varepsilon_{max.}$ 4·07 and 4·53, respectively; log $\varepsilon_{infl.}$ 3·99). In 0·001N-NaOEt maxima occurred at 253, 290 (very broad), and 444 mμ (log ε 4·21, 4·16, and 4·58, respectively).

2′ : 4-Dihydroxy-4′-methoxychalkone is a major pigment constituent of *X. australis* resin with an R_F about 0·8 (Whatman No. 1 and benzene). The spot on paper was yellow in daylight, orange-brown in ultra-violet light, and in the presence of ammonia vapour deep yellow and golden-yellow, respectively. Hydrochloric acid (4 : 1, concentrated hydrochloric acid and ethanol) produced an orange colour which faded to yellow on warming. When its alcoholic solution containing a little boric acid and a drop of hydrochloric acid was evaporated to dryness, a red residue was left, which became blue with sodium hydroxide.

Paeonol from 2′ : 4-*Dihydroxy*-4′-*methoxychalkone.*—2′ : 4-Dihydroxy-4′-methoxychalkone (0·106 g.) and potassium hydroxide (0·5 g.) in water (3 ml.) were gently refluxed for 6 hr., then acidified with 10N-sulphuric acid, and the liberated paeonol was steam-distilled. The distillate (15 ml.) was extracted with ether; the residue from the ether extract (0·051 g.) after crystallisation melted at 50—51°.

The author expresses his gratitude to Prof. H. Raistrick, F.R.S., for authentic samples of chrysophanic acid and its diacetyl derivative.

DIVISION OF INDUSTRIAL CHEMISTRY,
COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION,
BOX 4331, G.P.O., MELBOURNE. [*Received, March 9th*, 1954.]

The Distribution of Ruthenium Tetroxide between Carbon Tetrachloride and Aqueous Alkali, Acid, and Neutral Salt Solutions.

By F. S. MARTIN.

[Reprint Order No. 5214.]

Vapour-pressure and distribution measurements show that solutions of ruthenium tetroxide in water and carbon tetrachloride are ideal below 0·2M. The presence of neutral salts "salts-out" ruthenium tetroxide in a manner exactly analogous to that of other non-polar non-electrolytes, *e.g.*, benzene. Distribution experiments using dilute alkalis show that the tetroxide behaves as a weak acid with dissociation constant for the first hydrogen ion of $6·8 \pm 0·3 \times 10^{-12}$ in aqueous solution. Similar experiments with dilute acids indicate that it is probably also a very weak base of dissociation constant about $5·7 \times 10^{-15}$. The acid dissociation constant is discussed in connection with the probable structure of RuO_4, using Kossiakoff and Harker's theory of inorganic oxy-acids as modified by Ricci (*J. Amer. Chem. Soc.*, 1948, **70**, 109).

REDUCTION of ruthenium tetroxide in carbon tetrachloride solutions produces bi- or tri-nuclear products (*J.*, 1952, 2682; and unpublished work). Since one would expect a symmetrical covalent molecule such as ruthenium tetroxide to be non-associated in carbon

tetrachloride solution, it is of interest to verify that such polynuclear products are not the result of " pre-association " in solution. This may be done by both vapour-pressure and distribution studies. The analogous osmium tetroxide was examined in this manner by Anderson and Yost (*J. Amer. Chem. Soc.*, 1938, **60**, 1822) who concluded that their results indicated the existence of $(OsO_4)_4$ aggregates in carbon tetrachloride solution. Hildebrand and Scott (" Solubility of Non-Electrolytes," Reinhold Publ. Corp., New York, 1950, p. 220) however pointed out that the assumption of polynuclear species is unnecessary and that the observed deviations from ideality are satisfactorily explained on the basis of the difference in internal pressure of solute and solvent. By its distribution between carbon tetrachloride and aqueous alkalis osmium tetroxide was shown by Yost and White (*ibid.*, 1928, **50**, 81) to behave as a weak acid with dissociation constant 8×10^{-13} for the first hydrogen ion in aqueous solution. There is no reported study of ruthenium tetroxide solutions except a very brief mention that its acid dissociation constant is $1{\cdot}3 \times 10^{-12}$ (Silverman and Levi, Amer. Chem. Soc. 118th Meeting, 1950).

Since polynuclear products may be obtained by reducing dilute solutions (~0·1M) of ruthenium tetroxide in carbon tetrachloride, the present investigation has been confined to this low concentration range. More concentrated solutions have an unfortunate

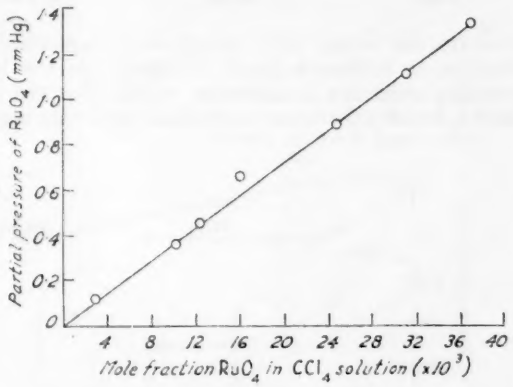


FIG. 1. *The partial pressure of* RuO_4 *in* CCl_4 *solutions at* 30°.

tendency to decompose to give ruthenium dioxide. The effect of neutral salts on the activity coefficient of ruthenium tetroxide in aqueous solution (" salting-out ") and the slight basic properties have been examined by distribution between carbon tetrachloride and aqueous acids.

(*a*) *Vapour-pressure Measurements.*—The vapour pressure of ruthenium tetroxide in equilibrium with carbon tetrachloride solutions at 30° ± 0·1° was measured by a transpiration method over the concentration range 0—0·2M. Fig. 1 shows that the vapour pressure of the tetroxide is strictly proportional to its mole fraction in the liquid phase in this range and therefore Henry's law is obeyed. There is thus no detectable degree of association in these solutions below 0·2M.

(*b*) *Distribution between Water and Carbon Tetrachloride.*—This was measured over an approximately twenty-fold concentration range at 20°. The results in Table 1 show that there is no appreciable variation in the distribution coefficient D, whose mean value is

TABLE 1. *The distribution of ruthenium tetroxide between carbon tetrachloride and water at* 20°.

A, Molarity of RuO_4 in CCl_4 phase	B, Molarity of RuO_4 in H_2O phase	$D = A/B$	A, Molarity of RuO_4 in CCl_4 phase	B, Molarity of RuO_4 in H_2O phase	$D = A/B$
$11{\cdot}9 \times 10^{-2}$	$2{\cdot}05 \times 10^{-3}$	58·1	$5{\cdot}25 \times 10^{-2}$	$9{\cdot}00 \times 10^{-4}$	58·4
$6{\cdot}63 \times 10^{-2}$	$1{\cdot}15 \times 10^{-3}$	57·6	$3{\cdot}80 \times 10^{-2}$	$6{\cdot}30 \times 10^{-4}$	60·5
$5{\cdot}60 \times 10^{-2}$	$9{\cdot}60 \times 10^{-4}$	58·2	$5{\cdot}69 \times 10^{-3}$	$9{\cdot}64 \times 10^{-5}$	59·0
$5{\cdot}56 \times 10^{-2}$	$9{\cdot}70 \times 10^{-4}$	57·4			

58·4. Since the organic phase is ideal, the aqueous phase must also be virtually so, and there can be only negligible association or dissociation of the solute.

(*c*) *Distribution between Dilute Aqueous Alkali and Carbon Tetrachloride.*—By an argument analogous to that used for osmium tetroxide (Yost and White, *loc. cit.*), it is shown that the acid dissociation constant of ruthenium tetroxide is given by $K_a = K_w(D - D')/[OH^-]D'$, where D is the distribution coefficient from pure water into carbon tetrachloride and D' that from the hydroxide solution whose concentration is given by $[OH^-]$. Table 2 presents values of K_a calculated by the above equation with $D = 58{\cdot}4$, which are satisfactorily constant, the mean being $6{\cdot}8 \pm 0{\cdot}3 \times 10^{-12}$. For hydroxide

TABLE 2. *Distribution of ruthenium tetroxide between carbon tetrachloride and sodium hydroxide solutions.*

Aqueous phase, [NaOH] (10^{-3} M)	$[RuO_4]_{CCl_4}$ (M)	$[RuO_4]_{aq.}$ (10^{-3} M)	D	$10^{12}K_a$
0·943	0·128	3·59	35·6	6·7
0·943	0·120	3·42	35·1	6·9
0·943	0·0427	1·19	36·0	6·5
1·886	0·0435	1·72	25·3	6·8
1·886	0·0377	1·51	25·0	7·0
9·43	0·0287	3·64	7·9	6·7

concentrations below 0·01N results were reproducible, but in more alkaline solutions reduction to ruthenate slowly occurred. As the hydroxide concentration approached normality reduction became very rapid. For the low hydroxide-ion concentrations in Table 2, activity coefficient corrections have been neglected.

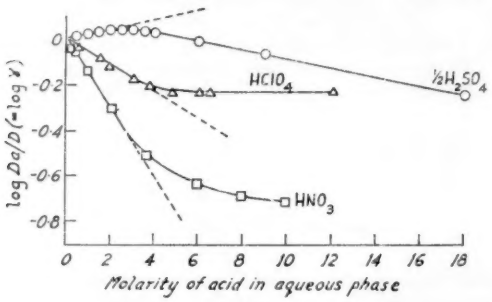


FIG. 2. *The distribution of* RuO_4 *between* CCl_4 *and aqueous acids.*

(*d*) *Distribution between Aqueous Neutral Salt Solutions and Aqueous Acids, and Carbon Tetrachloride.*—If the formation of acid in aqueous ruthenium tetroxide is due to the combination of solute and solvent, *e.g.*, $RuO_4 + H_2O \rightleftharpoons H_2RuO_5 \rightleftharpoons H^+ + HRuO_5^-$, there also exists the possibility of basic character, *e.g.*, $H_2RuO_5 \rightleftharpoons HRuO_4^+ + OH^-$. Distribution experiments similar to those reported in the previous paragraph, but using acids in the region of 0·01M, revealed no prominent decrease in D. However, as the acid concentrations were increased D decreased significantly. The experimental results for sulphuric, nitric, and perchloric acids are presented in Fig. 2, in the form of log D_a/D where D_a is the distribution coefficient for the aqueous solution. These results do not categorically indicate the presence of basic properties in ruthenium tetroxide since for these high electrolyte concentrations salting-out effects become prominent. Should aqueous acids have negative salting-out effects (salting-in) towards ruthenium tetroxide, the decrease (if any) in D_a due to acid–base interaction would be enhanced. Many theories have been advanced to account for salting-out effects on non-electrolytes (see McDevit and Long, *J. Amer. Chem. Soc.*, 1952, **74**, 1773; *Chem. Reviews*, 1952, **51**, 119) but none of these can predict with sufficient accuracy the quantitative salting-out effect to allow for this in the present case. However, comparison of the salting-out of ruthenium tetroxide by neutral salts with that of other non-polar non-electrolytes, *e.g.*, benzene (data from McDevit and Long, *loc. cit.*), shows that it follows the same general rules, *i.e.*, for electrolytes with a

common anion the salting-out effect decreases in the order $Na^+ > K^+ > Li^+ > H^+$, and the effects of the different ions seem to be additive. Hence by comparing the decrease in salting-out efficiency in this series for ruthenium tetroxide with that for benzene, it is possible to observe any abnormal decrease on passing from Li^+ to H^+ for ruthenium tetroxide.

The simple Setchenow equation for the salting-out effect of electrolytes on non-electrolytes, when modified for distribution experiments, becomes $\log D_a - \log D = kc$, where D_a is the distribution coefficient of the non-electrolyte from aqueous solution of electrolyte concentration c, and k is the salting-out coefficient. D_a is proportional to the activity coefficient of the non-electrolyte in the aqueous phase; for dilute solutions in pure water this may be taken as unity. Hence we also have $\log \gamma = kc$ where γ $(= D_a/D)$ is

FIG. 3. *Salting-out of* RuO_4 *by alkali-metal nitrates.*

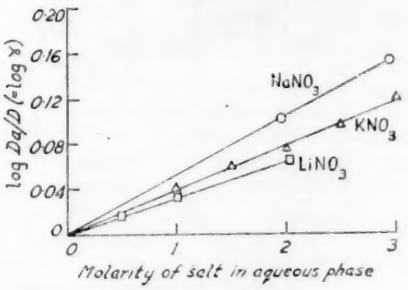


FIG. 4. *Salting-out of* RuO_4 *by alkali-metal chlorides.*

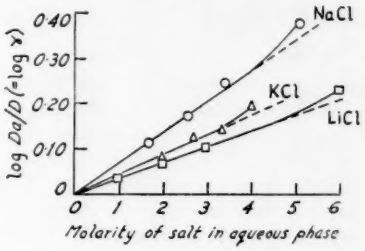
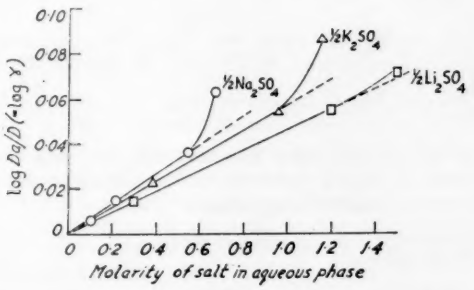


FIG. 5. *Salting out of* RuO_4 *by alkali-metal sulphates.*



the activity coefficient of non-electrolyte in aqueous solution containing electrolyte concentration c.

The results of distribution experiments for ruthenium tetroxide between carbon tetrachloride and aqueous phases containing alkali-metal nitrates, chlorides, and sulphates are presented in Figs. 3, 4, and 5. As usual the most linear plot for $\log \gamma$ against kc is obtained when c is expressed in terms of normalities. Taking the values of k for the acids as the limiting slopes as $c \longrightarrow 0$ in Fig. 1, the graphical presentation of salting-out coefficients in Figs. 6 and 7 shows that k for nitric acid is abnormally low, and probably also for perchloric acid (the alkali perchlorates were not studied because of the insolubility of the potassium salt). There is thus some indication of chemical interaction in these two cases. Whereas salting-out is not primarily affected by the activity coefficient of the salt (or acid), chemical interaction is, and this explains the apparent lack of interaction in the case of sulphuric acid whose activity coefficients are decidedly lower than those for nitric and perchloric acids at comparable concentrations. Fig. 2 shows, however, that interaction becomes prominent for sulphuric acid at concentrations above normal. Fig. 7 shows that the true salting-out coefficient for nitric acid would have a value of approximately 0·01 and an estimate of the chemical interaction may be made.

The basic dissociation constant of ruthenium tetroxide in water is given by $K_b = K_w(D_a - D')/[H^+]D'$, but D_a must be corrected for salting-out by the relation $\log D_a - \log D = kc$. For nitric acid, putting $k = 0{\cdot}01$, and applying the appropriate hydrogen-ion

FIG. 6. *Comparison of salting-out coefficients of RuO_4 for anions having common cations.*

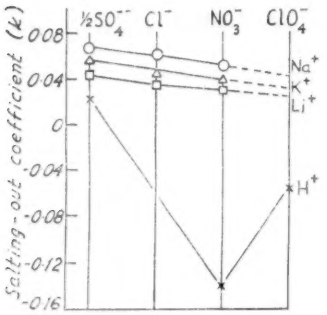
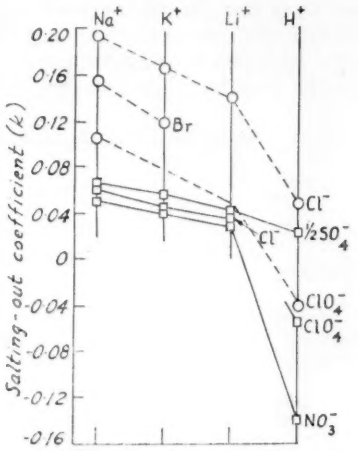


FIG. 7. *Comparison of salting-out coefficients for cations having common anions.*



– – – – Data for C_6H_6 (McDevit and Long).
——— RuO_4 results.

activity coefficient corrections (data from Conway, "Electrochemical Data," Elsevier Publ. Co., London and Amsterdam, 1952), the following values of K_b are obtained:

Molarity of HNO_3 in aqueous phase	0·25	0·5	0·75	1·0	1·5	2·0
$10^{15}K_b$	5·4	6·0	5·2	6·1	5·9	6·5

In view of the approximate corrections involved, the values of K_b are reasonably constant, the mean being $5{\cdot}7 \pm 0{\cdot}8 \times 10^{-15}$. For sulphuric acid the values are less consistent but of the same order of magnitude:

Molarity of H_2SO_4 in aqueous phase	1·75	2·0	2·5	3·0
$10^{15}K_b$ for RuO_4	3·8	4·6	6·6	7·6

It is impossible to make a salting-out correction for perchloric acid since the requisite data are not available. Fig. 7 shows that it would probably be small and the following values of K_b are obtained without making any salting-out corrections:

Molarity of $HClO_4$ in aqueous phase	0·5	0·75	1·0	1·5	2·0
$10^{15}K_b$ for RuO_4	2·8	3·1	3·0	2·9	2·7

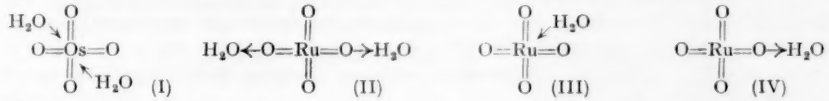
The values of K_b are again of the same order but the steady drift in values probably reflects the absence of the salting-out correction.

DISCUSSION

Ruthenium tetroxide resembles its analogue, osmium tetroxide, in displaying slight acidic properties in aqueous solution. However, although salts of diperosmic acid of the type $2MOH,OsO_4$ (Tschugaev, *Compt. rend.*, 1918, **167**, 162; Krauss and Wilken, *Z. anorg. Chem.*, 1925, **145**, 151) have been prepared, the preparation of corresponding ruthenium salts is precluded by the very ready reduction to ruthenate in the presence of alkalis. For osmium, Sidgwick ("Chemical Elements and Their Compounds," Oxford Univ. Press, 1950, p. 1507) considers that a covalency of ten is possible, and that acid formation by osmium tetroxide occurs by co-ordination of two water molecules to the central atom as in (I). The

circumstances may of course be similar for RuO_4, but there is no experimental evidence that this is so for either case.

Contrary to the results of measurements on osmium tetroxide by Brockway (*Rev. Mod. Physics*, 1936, **8**, 260) the bond lengths in both it and ruthenium tetroxide have been found by Braune and Stute (*Angew. Chem.*, 1938, **51**, 528) not to be equal. Braune and Stute have found that the bond lengths in each case go in two equal pairs, the lengths for ruthenium tetroxide being 1·66 and 1·01 Å. The fact that two of the oxygen atoms are thus bonded differently from the other two suggests that the formation of diperruthenic acid may occur by co-ordination of two water molecules through two oxygen atoms rather than to the central atom, *e.g.*, (II). According to this formulation, the central atom maintains its maximum covalency of eight, and two of the oxygen atoms increase their co-ordination numbers to two.



This structure is supported by the connection between the structure of inorganic oxy-acids and their dissociation constants. This was discussed by Kossiakoff and Harker (*J. Amer. Chem. Soc.*, 1938, **60**, 2047) who were able to predict with marked success the pK's of a number of non-resonating inorganic oxy-acids. Their method of calculation was cumbersome, however, and Ricci (*ibid.*, 1948, **70**, 109) showed that a modified simple equation, $pK = 8 - 9m + 4n$, gave good results for acids of the type H_aMO_b, where m = formal charge on the nucleus and n = number of non-hydroxyl oxygen atoms in the acid molecule. The theory is really limited to non-resonating non-metallic inorganic acids, but since it seems to apply to such acids as H_4GeO_4, where the metal germanium displays covalent characteristics, it may also be applicable to H_2RuO_5 where the ruthenium behaviour is predominantly covalent.

Assuming that the Ricci equation is applicable, we have for H_2RuO_5, $-\log(7 \times 10^{-12}) = 8 - 9m + 4n$. The number of non-hydroxyl oxygen atoms (n) is taken as four. Substitution in the equation then shows that the nearest whole number value for m is $+1$. This is the formal charge on the nucleus. For the structure (III), the formal charge on the nucleus is -1 and therefore this structure would seem to be ruled out. For the other structure (IV), however, the formal charge on the central ruthenium atom is zero, but that on the appropriate oxygen atom is $+1$. In fact the whole nucleus has a small positive charge in this case, and the structure is more consistent with the Kossiakoff–Harker–Ricci theory.

Experimental

Pure, dry, solutions of ruthenium tetroxide in carbon tetrachloride were prepared as described previously (Martin, *loc. cit.*).

Vapour-pressure Measurements.—A standard transpiration method, in which the same stream of carrier gas is passed successively through pure solvent and solution, was used as described by Glasstone "Textbook of Physical Chemistry," MacMillan and Co., London, 1946, p. 706). A special equilibration cell was designed (Fig. 8) to facilitate equilibrations with small amounts of solution. The cell consisted of four units, each holding 2—3 ml. of solution. The carrier gas (dry air) passed through each unit in turn, the first three units acting effectively as presaturators so that the composition of the solution in the fourth unit was not detectably changed during a run. The temperature was controlled at 30° ± 0·1°. The vapours were removed from the gas by passing it through weighed traps cooled in a solid carbon dioxide–trichloroethylene slurry. By passing the carrier gas at about 10 ml. per min., about 0·5 g. both of pure carbon tetrachloride and of carbon tetrachloride–ruthenium tetroxide condensed in the traps in 15 min. This was ample for determination of the ruthenium tetroxide concentration.

Equilibration.—Equal volumes (usually 2 ml.) of the requisite carbon tetrachloride and aqueous phases were thoroughly stirred for 10 min. The phases were separated cleanly by brief centrifuging, and aliquot portions were withdrawn for analysis.

Analysis.—Distribution ratios were determined (*a*) by conversion of ruthenium tetroxide into potassium ruthenate, and colorimetric determination, or (*b*) by β-particle counting of

preparation labelled with ^{106}Ru. In the first case, aqueous solutions (containing either acid or dilute alkali) of ruthenium tetroxide were made strongly alkaline (>2M) by the addition of solid potassium hydroxide. This converts the oxide into ruthenate: $2KOH + RuO_4 = K_2[RuO_4] + H_2O + \frac{1}{2}O_2$. After the solution had been made up to volume and freed from precipitate (centrifuge) (*e.g.*, K_2SO_4 from concentrated sulphuric acid solutions), the ruthenate colour was measured on a "Spekker" photometer with a combination of Wratten 50 and OB2 filters. Carbon tetrachloride solutions were shaken with 2M-potassium hydroxide, the

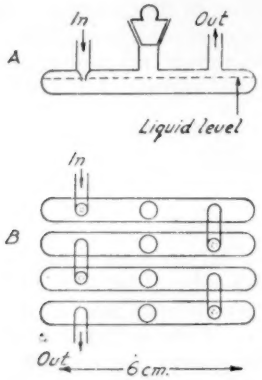


FIG. 8. RuO_4/CCl_4 *liquid–vapour equilibration apparatus for transpiration experiments.*

A, Unit equilibrator (side view).
B, Equilibrator consisting of four units in series (top view).

ruthenium being rapidly and completely extracted into the aqueous phase as ruthenate. The solution was then made up to volume, and its colour was measured.

In the second case, the radioactive solutions (either aqueous or in carbon tetrachloride) were pipetted on to small aluminium trays containing 1—2 drops of methanol. Immediate reduction to ruthenium dioxide occurred. A small amount of dilute collodion solution was added, and excess of solvent removed under an infra-red lamp. The samples were counted by using an end-window Geiger–Müller counter.

ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, BERKS.

[*Received, March 18th*, 1954.]

Synthetic Œstrogens. Part II. The Synthesis of Tetra-alkyldibenzyls and Substituted Succinonitriles by Free-radical Dimerisation.*

By R. L. HUANG and LEE KUM-TATT.

[Reprint Order No. 5243.]

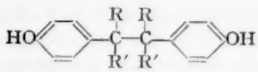
During the synthesis of the diphenols (I; R = Me, R′ = Et; R = R′ = Et and Pr^n; R = Me, R′ = Pr^n; and R = Et, R′ = CN) for tests as œstrogens, a study was made of the free-radical dimerisation of arylalkanes Ar·CHRR′ and alkylated benzyl cyanides CHRPh·CN, which formed the key reaction in the above synthesis. It was found that with the alkanes dimerisation was successful only if the side chain CHRR′ contained not more than four carbon atoms, whereas the benzyl cyanides with R = methyl to *n*-butyl dimerised normally, though in decreasing yields. This result is explained in terms of the stability of the intermediate free radicals. The limited application of the free-radical method in the former case necessitated the use of a different preparative method for the second, third, and fourth substances mentioned above.

DIMERISATION of free radicals appears particularly well suited to the synthesis of fully substituted dibenzyls of the general structure (I) and has been applied in the present

* Part I, *J.*, 1953, 160.

investigation to the synthesis of (i) tetra-alkyldibenzyls (I; R, R′ = alkyl) and (ii) substituted succinonitriles (I; R = alkyl, R′ = CN) in a study of the relation between chemical structure and œstrogenic activity.

Tetra-alkyldibenzyls.—In Part I (*loc. cit.*) the synthesis of 2 : 3-di-*p*-hydroxyphenyl-2 : 3-dimethylbutane (I; R = R′ = Me) by the dimerisation of 2-arylpropanes was described.* The higher homologues (i) *meso*- and racemic (I; R = Me, R′ = Et), (ii) (I; R = R′ = Et), (iii) (I; R = Me, R′ = Pr^n), and (iv) (I; R = R′ = Pr^n) have now been prepared. Of these the first appears to be of particular biological interest in view of (*a*) the structural relation it bears to hexœstrol and to 3 : 4-di-*p*-hydroxyphenyl-3-methylhexane recently reported by Dodds, Huang, Lawson, and Robinson (*Proc. Roy. Soc.*, 1953, *B*, **140**, 470), and (*b*) the possibility of its existing in a *meso*- and a racemic modification, which would facilitate a study of the stereochemical relation with biological activity. A study of the synthesis of these higher homologues incidently revealed the limitations of the free-radical method, which was found applicable only to the synthesis of the first diphenol (I; R = Me, R′ = Et). For the preparation of the other homologues it was necessary to employ a totally different method, involving bimolecular reduction of the appropriate alkylarylcarbinols.



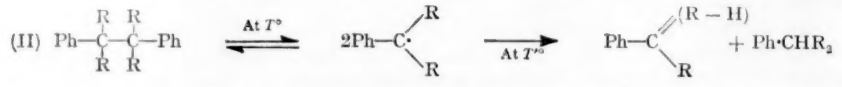
(I)

In attempts to prepare (I; R = Me, R′ = Et; and R = R′ = Et) by the dimerisation method previously described, 2-*p*-methoxyphenylbutane and 3-*p*-methoxyphenylpentane, respectively, were each treated with di-*tert.*-butyl peroxide at 140°. Contrary to expectation, however, apart from polymeric material, none of the desired dimers could be isolated from the product by chromatography, distillation, or recrystallisation. Similarly, 3-*p*-benzoyloxyphenylpentane failed entirely to dimerise in the desired manner (Morsingh, Thesis, Malaya, 1952). This failure of the intermediate free radicals to dimerise was attributed to their instability at the reaction temperature, as a result of which disproportionation became the main reaction and the corresponding styrene so produced underwent additive polymerisation in the presence of *tert.*-butoxy-radicals. Since, according to accepted theory (Ingold, *Trans. Faraday Soc.*, 1934, **30**, 52; cf. Huang, *J.*, in the press) electropositive substituents, such as the *p*-methoxy-group, destabilise free radicals of the type under consideration, the unsubstituted radicals PhEtMeC· and $PhEt_2C$· should be relatively stable and therefore less prone to disproportionation. This was found to be so in the former case, and dimerisation of 2-phenylbutane in the usual manner did afford in fair yields approximately equal quantities of the *meso*- and racemic 3 : 4-dimethyl-3 : 4-diphenylhexanes, the less soluble and higher-melting isomer being assigned the *meso*-configuration. Nitration of these by an improved method, followed by reduction and a diazo-reaction (as in Part I), furnished the required *meso*- and racemic diphenols (I; R = Me, R = Et). However, with the latter radical, $PhEt_2C$·, derived from 3-phenylpentane, disproportionation was again found to be predominant. Two attempts were accordingly made to stabilise this free radical, *viz.*, (*a*) by the introduction of an electronegative substituent, and (*b*) by operating at a lower temperature. Both proved ineffective. Thus, 3-*p*-nitrophenylpentane on reacting with di-*tert.*-butyl peroxide at 140° similarly gave an intractable product, while the use of acetyl peroxide as the dimerising agent, for which a reaction temperature of 80° suffices (Kharasch, McBay, and Urry, *J. Org. Chem.*, 1945, **10**, 401), also failed. It becomes clear, therefore, that increase in the length of the carbon chain causes a sharp decline in the thermal stability of the free radicals of this type, and hence this method of synthesis of tetra-alkyldibenzyls is limited to the lower homologues, involving the formation of free radicals with a carbon chain of not more than four carbon atoms.

Ziegler and Deparade (*Annalen*, 1950, **567**, 123) recently studied the thermal stability

* In this paper, the conversion of X·H into X_2 is referred to, inaccurately but conveniently, as dimerisation; and the substances X·H and X_2 similarly as monomer and dimer, respectively.

of various symmetrical tetra-alkyldibenzyls (II; prepared by another method) and found that these dissociate into free radicals as follows:



the temperatures of appreciable decomposition T being: R = Me, 240°; R = Et, 142°; R = Pr^n, 110°. The failure of 3-phenylpentane to dimerise at 140° is therefore not surprising. However, it is to be noted that T is not necessarily the same as the temperature T' at which disproportionation of the resulting radicals becomes appreciable, and that the latter can be equal to, or might well be lower than T. This is clearly seen in the case of (II; R = Et) for which T is 142°, but T' is not more than 80° from the experiment using acetyl peroxide described above. Furthermore, since it is generally known that reactive free radicals normally undergo rapid reactions such as hydrogen abstraction, substitution, and disproportionation, whereas dimerisation is a comparatively much slower process characteristic of relatively stable radicals (cf. Kharasch and Buchi, *J. Amer. Chem. Soc.*, 1951, **73**, 632; Kharasch, Kane, and Brown, *ibid.*, 1942, **64**, 1621), the yield of the desired type of dimer compared with that of polymers might be taken as a rough indication of the relative stability of the free radicals. Thus in the cases so far encountered, the products range from a high yield in the case of cumene of almost pure dimer, which readily crystallised from the reaction mixture, to a much lower yield in the case of 2-*p*-methoxyphenylpropane of a product contaminated with by-products removed only after chromatography (Part I, *loc. cit.*). Assessed in this way, some of the free radicals can be arranged in decreasing relative stability as follows: $PhMe_2C\cdot > PhMeEtC\cdot > p\text{-}MeO\cdot C_6H_4\cdot CMe_2\cdot > PhEt_2C\cdot$.

The higher homologues (I; R = R′ = Et; R = Me, R′ = Pr^n; and R = R′ = Pr^n) were prepared by a modification of the method by which Klages synthesised 2 : 3-dimethyl-2 : 3-diphenylbutane (*Ber.*, 1902, **35**, 2638; cf. Ziegler and Deparade, *loc. cit.*), namely, by the reduction of 2-phenylpropan-2-ol with zinc and hydrogen iodide in acetic acid. Although the yield was low, the synthesis was a short one. Thus the crude alcohols 3-*p*-methoxyphenylpentan-3-ol, 2-*p*-methoxyphenylpentan-2-ol, and 4-*p*-methoxyphenylheptan-4-ol, obtained from the appropriate Grignard reactions, were each reduced according to Klages's method, and the resulting products demethylated directly with hydriodic acid in acetic acid at 80°, yielding the required diphenols. Only one of the two possible isomers (I; R = Me, R′ = Pr^n) was obtained, presumably the *meso*-isomer. The failure of such dimerisation by classical methods to give both isomers, when such are capable of existence, has often been encountered, and reflects on the advantage of free-radical methods whenever applicable.

Of the tetra-alkyldibenzyls synthesised above which were subjected to a Zeisel methoxy-determination, all exhibited the same anomalous behaviour as described for the tetramethyl derivatives reported in Part I.

Substituted Succinonitriles.—The free radicals derived from alkylated benzyl cyanides (III) appeared worthy of study for a comparison with the free radicals already investigated, since the former type are further stabilised by a cyano-group. From the point of view of œstrogens, our approach was mainly stereochemical, namely, the preparation of the *meso*- and racemic series of the homologous succinonitriles (I; R = alkyl, R′ = CN), by the free-radical method, which has been shown to be distinctly successful in the preparation of such isomers. Further biological interest in these succinonitriles lies in their possible conversion into the corresponding succinic acids, one member of which (I; R = H, R′ = CO_2H) has recently been reported to be highly potent (Hoch, *Compt. rend.*, 1950, **231**, 625).

The free-radical dimerisation of substituted benzyl cyanides (III) does not appear to have been studied previously and was therefore investigated in some detail. Dimerisation by the usual method of (III; R = Me, Et, Pr^n, or Bu^n), best prepared by alkylation of benzyl cyanide with sodamide, gave varying yields of mixtures of the *meso*- and racemic

(III) Ph·CHR(CN) PhR(CN)C·C(CN)RPh (IV)

dimers (IV), the less soluble and higher-melting isomer in each case being assigned the *meso*-configuration. As expected, the lower homologues (III; R = Me, Et) gave good yields of the respective *meso*- and racemic dimers, uncontaminated by any impurities or polymeric materials. With increase in the length of the carbon chain (R = Pr^n, Bu^n) polymeric substances increased with a resulting diminution in yield of the dimer, although this diminution was much less pronounced than in the alkylbenzene series. This result is to be attributed to the stabilising influence of the cyano-group.

As an œstrogen the diphenol (I; R = Et, R′ = CN) has already been reported by Niederl and Ziering (*J. Amer. Chem. Soc.*, 1942, **64**, 2486) whose synthesis involves the dimerisation of the sodio-derivative of *p*-nitrophenylbutyronitrile with iodine. No experimental details or yields were given, and only one of the two isomers, presumably the *meso*-, was obtained. In an attempt to synthesise both isomeric diphenols, the *meso*- and the racemic dimer (IV; R = Et) obtained as described above were separately subjected to nitration and reduction, and each of the resulting diamines was diazotised in pyridine in the manner already described. Only one diphenol, m. p. 225—226°, was obtained, however, and it seems likely that one of the isomers (probably the racemic) had suffered isomerisation under the conditions of the decomposition of the diazo-compound. This diphenol differed from that reported by Niederl and Ziering, m. p. 218° (although their intermediate dinitro- and diamino-compounds agreed in m. p. with our higher-melting series), but it is evident that theirs is an impure sample since it gave an incorrect elemental analysis. In the course of this work it was also found that the usual methods of nitration, reduction, and diazotisation (*e.g.*, nitric acid at 60°; iron filings or zinc or tin and hydrochloric acid in ethanol; and diazotisation in aqueous sulphuric acid, respectively) gave poor results. For all these operations methods which give reasonable yields have been worked out.

Hydrolysis of the cyano-groups in (IV; R = Et) was attempted by (*a*) refluxing with 70% sulphuric acid in ethanol, (*b*) prolonged contact with concentrated sulphuric acid at room temperature (28°), and (*c*) refluxing with 40% aqueous potassium hydroxide. All proved unsuccessful, the starting material in each case being totally recovered, although the last reagent was effective in the hydrolysis of tetramethylsuccinonitrile (Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 312).

Experimental

The 3 : 4-*Dimethyl*-3 : 4-*diphenylhexanes.*—(*a*) *sec.*-Butylbenzene (47 g.) and di-*tert.*-butyl peroxide (36 g., Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205) were heated under reflux at 140—150° for 48 hr. Distillation removed the volatile fractions (19 g.) and the unchanged hydrocarbon, b. p. 34—36°/2 mm. (30 g.). The residue on distillation gave fractions: (i) b. p. 122°/0·5 mm. (8·1 g.), (ii) b. p. 135°/0·5 mm. (5·0 g.), (iii) b. p. 180—187°/0·5 mm. (2·2 g.), and (iv) b. p. 220—230°/0·5 mm. (2·1 g.). Fractions (i) and (ii) partially crystallised, yielding a solid, m. p. 54—59°, very soluble in benzene, but less so in *cyclo*hexane and light petroleum. It was crystallised from methanol, giving meso-3 : 4-*dimethyl*-3 : 4-*diphenylhexane*, prisms, m. p. 93° (5·5 g.) (Found: C, 90·2; H, 10·1; OMe, 2·6. $C_{20}H_{26}$ requires C, 90·2; H, 9·8; OMe, 0%). The mother-liquors were combined, concentrated, and distilled, yielding a nearly colourless viscous oil, b. p. 135—138°/0·5 mm. (6·0 g.). This crystallised on chilling, giving *racemic* 3 : 4-*dimethyl*-3 : 4-*diphenylhexane*, m. p. 40—41° (Found: C, 89·8; H, 9·6; OMe, 2·2%). Attempts to induce crystallisation in fractions (iii) and (iv) failed.

(*b*) *sec.*-Butylbenzene (16·5 g.) and di-*tert.*-butyl peroxide (13·5 g.) were heated in a sealed tube at 150° for 24 hr. Distillation of the product afforded a colourless viscous liquid, b. p. 126—147°/1 mm. (6·4 g.), separable by fractional crystallisation into the *meso*- (2·4 g.) and the racemic (2·6 g.) isomer as described above.

meso-3 : 4-*Dimethyl*-3 : 4-*di*-p-*nitrophenylhexane.*—Finely powdered *meso*-3 : 4-dimethyl-3 : 4-diphenylhexane (m. p. 91°; 2·73 g.) was added during 3 hr. to fuming nitric acid (30 c.c.; *d* 1·515) at 0° with vigorous stirring. After 2 hours' more stirring the mixture was poured on chipped ice, and the yellowish solid which separated was filtered off and washed thoroughly with water. It was then dissolved in benzene and dried by azeotropic distillation of the solvent, yielding a light yellow solid, m. p. 195—198° (3·1 g.). Further recrystallisation furnished the pure *dinitro*-compound, m. p. 201—202° (Found: C, 67·2; H, 6·55; N, 7·7; OMe, 3·3. $C_{20}H_{24}O_4N_2$ requires C, 67·4; H, 6·7; N, 7·9; OMe, 0%). It was soluble in benzene, chloroform, and

dioxan but sparingly so in ethanol. This method of nitration was superior to that of Reinbach and Aaronson (*J. Amer. Chem. Soc.*, 1930, **52**, 5050) used in Part I, which gave a much lower yield (23%).

meso-3 : 4-*Di*-p-*aminophenyl*-3 : 4-*dimethylhexane*.—The above dinitro-compound (3·1 g.) on reduction with iron filings and hydrochloric acid in ethanol, as previously described, gave the *diamine*, which separated from benzene in prisms, m. p. 176° (1·2 g.) (Found: C, 80·9; H, 9·6; N, 9·3. $C_{20}H_{28}N_2$ requires C, 81·1; H, 9·5; N, 9·5%). It was soluble in *cyclo*hexane, and in dilute hydrochloric acid. Reduction by zinc and hydrochloric acid in dioxan was more convenient but gave a much reduced yield.

meso-3 : 4-*Di*-p-*hydroxyphenyl*-3 : 4-*dimethylhexane*.—The above diamine (1·0 g.) in pyridine (15 c.c.) was diazotised, and the resulting diazo-compound decomposed as described previously. The diphenol was thus obtained first as an oil (0·53 g.) and after five recrystallisations from benzene as woolly needles, m. p. 175° (0·13 g.) (Found: C, 80·5; H, 8·7; OMe, 1·8. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·7; OMe, 0%). It was soluble in aqueous potassium hydroxide but only slightly so in sodium hydroxide.

Racemic 3 : 4-*Dimethyl*-3 : 4-*di*-p-*nitrophenylhexane*.—Nitration of the racemic hydrocarbon (4·0 g.) by the method described above gave the *dinitro*-derivative, soluble in benzene and chloroform, m. p. 152° (2·4 g.) (Found: C, 67·1; H, 6·9%).

Racemic 3 : 4-*Di*-p-*aminophenyl*-3 : 4-*dimethylhexane*.—Reduction of the above dinitro-compound (1·75 g.) with iron filings and hydrochloric acid in ethanol yielded the diamine (1·1 g.), soluble in benzene and in *cyclo*hexane, and from a mixture of these solvents it crystallised in prisms, m. p. 149°; mixed m. p. with the dinitro-compound (of m. p. 152°), 137—142°. It was used directly for the next operation.

Racemic 3 : 4-*Di*-p-*hydroxyphenyl*-3 : 4-*dimethylhexane*.—The above diamine (0·80 g.) on diazotisation in the usual manner afforded the required *diphenol*, which crystallised from benzene–*cyclo*hexane in woolly needles, m. p. 156° (0·13 g.) (Found: C, 80·4; H, 8·9; OMe, 2·3%). It was soluble in aqueous potassium hydroxide but sparingly so in sodium hydroxide.

Attempted Dimerisation of 3-*Phenylpentane*.—Crude 3-phenylpentan-3-ol (108 g.), from ethyl benzoate and ethylmagnesium iodide, was heated with anhydrous oxalic acid (72 g.) and quinol (*ca.* 0·5 g.) at 120—130° for 3 hr., and the resulting olefin distilled (b. p. 54—55°/2 mm., n_D^{23} 1·5233; 63 g.). This was then catalytically hydrogenated (palladised strontium carbonate), giving the required hydrocarbon, b. p. 118°/80 mm., n_D^{23} 1·4973 (44 g.). Klages (*Ber.*, 1903, **36**, 693) reports n_{16} 1·4988. The pentane (43·5 g.) and di-*tert.*-butyl peroxide (28·2 g.) were heated together at 140—145° for 48 hr. After distillation of the unchanged material (31 g.), etc., a pale yellow residue (11·6 g.) remained which was very soluble in light petroleum, benzene, or ethyl acetate, but sparingly so in methanol. A portion of this (2·0 g.), dissolved in light petroleum, was chromatographed on alumina. Elution with benzene–light petroleum (1 : 5) gave eight fractions of viscous oils, none of which could be induced to crystallise. The main portion from the above was distilled, giving (*a*) b. p. 140—192°/1 mm. (3·7 g.), and (*b*) b. p. 200—220°/1 mm. (2·3 g.). These were further distilled evaporatively, giving samples the analyses of which showed them to contain approx. 5% of oxygen [Found, for (*b*): *M* (cryoscopic), 530. Calc. for dimer: *M*, 284]. In another experiment acetyl peroxide (3·7 g.; personal communication by Professor M. S. Kharasch), dissolved in 3-phenylpentane (16 g.), was added during 6 hr. to the same hydrocarbon (*ca.* 4 g.) held at 80—85°. The volatile fractions and unchanged hydrocarbon were then distilled *in vacuo* (temperature not exceeding 85°), and the residue (5·7 g.) was chromatographed as before, yielding none of the required dimer nor any crystalline material (Ziegler *et al.*, *loc. cit.*, report m. p. 42° for 3 : 4-diethyl-3 : 4-diphenylhexane).

Similar attempts to dimerise the following compounds with di-*tert.*-butyl peroxide failed: 3-*p*-nitrophenylpentane, 3-*p*-methoxyphenylpentane, 3-*p*-benzoyloxyphenylpentane, and 2-*p*-methoxyphenylbutane.

3 : 4-*Diethyl*-3 : 4-*di*-p-*methoxyphenylhexane* (cf. Klages, *loc. cit.*).—Crude 3-*p*-methoxyphenylpentan-3-ol (42 g., prepared from methyl *p*-anisate and ethylmagnesium bromide) was added in one portion with vigorous stirring to an externally cooled (ice) saturated solution of hydrogen iodide in glacial acetic acid (230 c.c.), followed by zinc dust (35 g.) in small portions, during 30 min. The solution changed in colour from red to pale yellow, with no appreciable evolution of heat. The mixture was poured on chipped ice, and after removal of the water and acetic acid under reduced pressure (temp. not exceeding 80°), the residue was diluted with water and extracted with ether. The ethereal extract was washed with dilute aqueous solutions of sodium hydrogen sulphite, sodium hydrogen carbonate, and sodium hydroxide, and finally with water, and dried. (The alkaline washings gave no phenolic matter on acidification.) Removal

of ether gave a light yellow oil (20 g.) which failed to crystallise and was used directly for the next operation. In another experiment the reaction mixture after addition of zinc was kept at room temperature (28°) for 72 hr. No appreciable demethylation took place.

3 : 4-*Diethyl*-3 : 4-*di*-p-*hydroxyphenylhexane*.—The crude hexane obtained as above (10 g.) was dissolved in a solution of hydriodic acid (50 c.c., *d* 1·74) in acetic acid (75 c.c.), and the mixture warmed at 80—85° for 72 hr. Water was added, the product taken into ether, washed with sodium hydrogen sulphite, sodium carbonate, and water, and the phenolic matter extracted into aqueous potassium hydroxide. Acidification followed by ether extraction and evaporation yielded a solid, m. p. 62—65° (7·1 g.), probably a mixture of the required diphenol and the monomer 3-*p*-hydroxyphenylpentane (m. p. 79—80°; Dianin, *Ber.*, 1892, **25**, 336). Fractional recrystallisations from benzene–*cyclo*hexane afforded 3 : 4-*diethyl*-3 : 4-*di*-p-*hydroxyphenylhexane* in woolly needles, m. p. 97—100° (3·1 g.), raised to 103—104° after further recrystallisations (Found : C, 80·8; H, 9·3; OMe, 2·0. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·2; OMe, 0%). It gave no colour with alcoholic ferric chloride, and exhibited the same solubilities in aqueous alkalis as the lower homologues. The *dibenzoate* (from dioxan) had m. p. 207° (Found : C, 80·4; H, 7·1. $C_{36}H_{38}O_4$ requires C, 80·9; H, 7·2%).

4 : 5-*Di*-p-*hydroxyphenyl*-4 : 5-*di*-n-*propyloctane*.—Crude 4-*p*-methoxyphenylheptan-3-ol (40 g.) (prepared from ethyl *p*-anisate and *n*-propylmagnesium iodide) was reduced with zinc (35 g.) and hydrogen iodide in acetic acid (250 c.c.) as previously described. A portion (9·0 g.) of the crude 4 : 5-di-*p*-methoxyphenyl-4 : 5-di-*n*-propyloctane (29·4 g.) was demethylated with hydriodic acid (45 c.c., *d* 1·74) in acetic acid (70 c.c.) in the usual manner, giving a viscous oil (7·4 g.) which was benzoylated directly, yielding 4 : 5-*di*-p-*benzoyloxyphenyl*-4 : 5-*di*-n-*propyloctane* as prisms, m. p. 178—181° (3·3 g.) raised after recrystallisation from benzene–ethyl acetate to 182° (Found : C, 81·2; H, 8·1; OMe, 2·4. $C_{40}H_{46}O_4$ requires C, 81·4; H, 7·8; OMe, 0%). (The monomer, 4-*p*-benzoyloxyphenylheptane has m. p. 29—30°; Dianin, *loc. cit.*) Hydrolysis of the dibenzoate with alcoholic potassium hydroxide yielded a diphenol, probably 4 : 5-di-*p*-hydroxyphenyl-4 : 5-di-*n*-propyloctane, obtained as needles (from benzene–*cyclo*hexane), m. p. 103—104°, which became pink and could not be obtained analytically pure.

4 : 5-*Di*-p-*hydroxyphenyl*-4 : 5-*dimethyloctane*.—Crude 2-*p*-methoxyphenylpentan-2-ol (7·5 g.) prepared from *p*-methoxyacetophenone (cf. Burton and Praill, *J.*, 1951, 726) and *n*-propylmagnesium iodide, on reduction followed by demethylation with the usual reagent yielded an oil (2·6 g.) which on treatment with benzene–light petroleum deposited the monomer 2-*p*-hydroxyphenylpentane, m. p. 72—73° (0·2 g.) (Found : *M*, 158. Calc. for $C_{11}H_{16}O$: *M*, 164). Benzoylation of the mother-liquor afforded a semi-solid which was exhaustively extracted with ethyl acetate. A solid remained, m. p. 247—250° (0·6 g.), which was insoluble in all the usual organic solvents, and attempts at recrystallisation failed. The ethyl acetate-soluble fraction on concentration yielded needles, m. p. 211—213° (0·4 g.). Recrystallisation from ethyl acetate–ethanol gave 4 : 5-*di*-p-*benzoyloxyphenyl*-4 : 5-*dimethyloctane*, m. p. 215—216° (Found : C, 80·8, 81·1; H, 7·2, 7·3. $C_{36}H_{38}O_4$ requires C, 80·9; H, 7·2%). It is sparingly soluble in ethanol and benzene but moderately so in dioxan.

Alkylation of Benzyl Cyanide.—Alkylation of benzyl cyanide with sodium ethoxide in ethanol or with sodium *iso*propoxide in *iso*propanol with the appropriate alkyl iodide both gave unsatisfactory results. Potassium *tert.*-butoxide in *tert.*-butanol gave fair but variable yields, satisfactory results being obtained only with pure reagents (Method A). The best reagent was found to be sodamide in benzene solution (Method B; cf. Bodroux and Taboury, *Bull. Soc. chim.*, 1910, **7**, 670). By the last two methods the following substituted benzyl cyanides were prepared (yields in parentheses) : α-phenylpropionitrile (Method A : 52%; Method B : 87%); α-phenylbutyronitrile (A : 64%; B : 80—85%); α-phenylvaleronitrile (A : 45%); α-phenylhexanonitrile (A : 39%; B : 70%). Baldinger and Nieuwland (*J. Amer. Chem. Soc.*, 1933, **55**, 2851) prepared the above benzyl cyanides by alkylation with sodamide in liquid ammonia.

Dimerisation of Substituted Benzyl Cyanides.—The usual methods were used, *viz.*, heating a mixture of the cyanide (1 mole) and di-*tert.*-butyl peroxide (0·6 mole) at 140—150° either under reflux for 48 hr. (method A) or in a sealed tube for 24 hr. (method B). At the end of the reaction the volatile material and the unchanged cyanide were removed by distillation under reduced pressure, and the less soluble dimer (the *meso*-modification) was induced to crystallise by addition of methanol. The more soluble isomer was obtained by fractional recrystallisation from the same solvent, or in some cases by distillation of the mother-liquors. α-Phenylpropionitrile (33·6 g.) when dimerised by method A gave (i) meso-2 : 3-*dicyano*-2 : 3-*diphenylbutane*, prisms (from methanol), m. p. 218—225° (4·7 g.) raised after recrystallisation from benzene to 224—225° (Found : C, 83·1; H, 6·1; N, 11·1. $C_{18}H_{16}N_2$ requires C, 83·1; H, 6·2; N, 10·8%);

and (ii) the racemic *isomer*, m. p. 133—135° (6·0 g.) raised to 143—144° after recrystallisation from methanol, from which it separated in prisms (Found: C, 83·2; H, 6·0; N, 10·8%).

α-Phenylbutyronitrile (24 g.) gave, by method A: (i) *meso*-3 : 4-dicyano-3 : 4-diphenylhexane, prisms (from methanol), m. p. 174—175° (5·3 g.) (Niederl and Ziering, *loc. cit.*, report m. p. 175°) (Found: C, 83·4; H, 7·0; N, 9·6; OMe, 0. Calc. for $C_{20}H_{20}N_2$: C, 83·3; H, 6·9; N, 9·7; OMe, 0%); (ii) the racemic *compound*, needles (from ethanol), m. p. 114—117° (3·8 g.) raised to 117—118° after further recrystallisations (Found: C, 83·4; H, 7·0; N, 9·6; OMe, 0%). By Method B, α-phenylbutyronitrile (20 g.) similarly gave the *meso*- (3·4 g.) and the racemic (4·3 g.) dimer.

α-Phenylvaleronitrile (10 g.) yielded by method B meso-4 : 5-*dicyano*-4 : 5-*diphenyloctane* (1·5 g.), prisms (from methanol), m. p. 171° (Found: C, 83·5; H, 7·6; N, 8·8. $C_{22}H_{24}N_2$ requires C, 83·6; H, 7·6; N, 8·9%). The mother-liquors were distilled, giving a liquid, b. p. 166—168°/1 mm. (2·4 g.), which yielded on crystallisation from methanol more of the *meso*-isomer (0·34 g.) and the racemic *isomer*, prisms (from methanol), m. p. 122—123° (1·24 g.) (Found: C, 83·4; H, 7·5; N, 8·8%). There was an undistillable residue (2·6 g.) from which no crystalline material could be obtained.

α-Phenylhexanonitrile (17·3 g.), when dimerised by method B, afforded meso-5 : 6-*dicyano*-5 : 6-*diphenyldecane*, prisms (from methanol), m. p. 133—135° (1·7 g.), raised to 137—138° on further recrystallisations (Found: C, 83·9; H, 8·4; N, 7·9. $C_{24}H_{28}N_2$ requires C, 83·7; H, 8·2; N, 8·2%). Distillation of the mother-liquors gave (i) a yellowish oil, b. p. 172—188°/2 mm. (4·4 g.), which probably contained mainly the racemic decane, and (ii) a residue (4·5 g.) which failed to crystallise. Redistillation of (i) gave a liquid, b. p. 160—165° (bath-temp./1 mm., n_D^{23} 1·5179 (Found: C, 83·7; H, 8·1; N, 8·5%), which did not crystallise.

meso-3 : 4-*Dicyano*-3 : 4-*di*-p-*nitrophenylhexane*.—Nitration of *meso*-3 : 4-dicyano-3 : 4-diphenylhexane (6·0 g.) with fuming nitric acid as described above gave the dinitro-compound, m. p. 217—218° (6·8 g.) raised to 223—225° by recrystallisation from chloroform–benzene (Niederl and Ziering, *loc. cit.*, report m. p. 225°). It was soluble in dioxan and chloroform, but sparingly so in ether, benzene, acetone, or ethanol.

meso-3 : 4-*Di*-p-*aminophenyl*-3 : 4-*dicyanohexane*.—Reduction of the dinitro-compound with iron filings and concentrated hydrochloric acid (Part I, *loc. cit.*) or with zinc or tin and hydrochloric acid in ethanol, gave poor results for both the *meso*- and the racemic dinitro-compound. The best procedure was found to be the following: concentrated hydrochloric acid (70 c.c.) was added during 2·5 hr. with vigorous stirring, at 20—25°, to a mixture of granulated tin (10 g.) and 3 : 4-dicyano-3 : 4-dinitrophenylhexane (3·7 g.) in dioxan (100 c.c.). The temperature was then raised to 50—60°, and stirring continued for 4 hr. The mixture was filtered, and on removal of the dioxan under reduced pressure the tin double salt of the diamine separated as a white solid. This was decomposed by addition of excess of 10% aqueous sodium hydroxide in the cold, the liberated diamine being then taken into ether. It was further purified by extraction into 2N-hydrochloric acid, precipitated therefrom with aqueous sodium hydroxide (20%), and again extracted into ether. Removal of the solvent gave *meso*-3 : 4-di-*p*-aminophenyl-3 : 4-dicyanohexane, which crystallised from benzene in prisms, m. p. 207—208° (2·1 g.) (Found: C, 75·3; H, 6·8. Calc. for $C_{20}H_{22}N_4$: C, 75·5; H, 6·9%). Niederl and Ziering (*loc. cit.*) report m. p. 208°.

meso-3 : 4-*Dicyano*-3 : 4-*di*-p-*hydroxyphenylhexane*.—Diazotisation of the above diamine (2·0 g.) in pyridine as already described yielded the diphenol, m. p. 214—218° (0·80 g.), obtained as prisms, m. p. 225—226°, on recrystallisation from benzene (Found: N, 8·7. Calc. for $C_{20}H_{20}O_2N_2$: N, 8·8%). Niederl and Ziering (*loc. cit.*) report m. p. 218°, and give N, 7·8%.

Racemic 3 : 4-*Dicyano*-3 : 4-*di*-p-*nitrophenylhexane*.—Nitration of the hydrocarbon (7·6 g.) with fuming nitric acid at 0—10° as previously described gave the required *dinitro*-compound, obtained as pale yellow prisms, m. p. 208° (softening slightly at 185°; 6·4 g.), after recrystallisations from chloroform and from benzene–ethanol (Found: C, 63·6; H, 5·0; N, 14·9. $C_{20}H_{18}O_4N_4$ requires C, 63·5; H, 4·8; N, 14·8%). A solution of this dinitro-compound in dioxan gave a faint pink colour with sodium hydroxide.

Racemic 3 : 4-*Di*-p-*aminophenyl*-3 : 4-*dicyanohexane*.—Reduction of the above dinitro-compound (6·0 g.) as described for the *meso*-isomer afforded the *diamine*, m. p. 182—184° (4·4 g.) raised to 188—189° by recrystallisation from benzene, from which it separated in almost colourless prisms (Found: C, 75·3; H, 7·0. $C_{20}H_{22}N_4$ requires C, 75·5; H, 6·9%). It was soluble in dioxan and benzene, and less so in ethanol and ether.

The diamine (2·5 g.) was diazotised as for the *meso*-isomer, yielding an oil (1·7 g.) which

crystallised in contact with benzene, then having m. p. *ca.* 212—214° raised on further recrystallisation to 225—226°, alone or mixed with the *meso*-diphenol obtained above.

The authors thank the Shell Company of Singapore, Ltd., for a research fellowship (to L. K. T.).

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, March 26th*, 1954.]

Preparation of Phenothiazine Derivatives as Possible Anthelmintics.

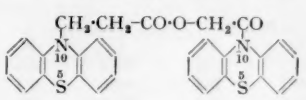
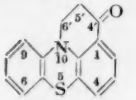
By ALEXANDER MACKIE and A. ANTHONY CUTLER.

[Reprint Order No. 5263.]

10-Aroyl derivatives of phenothiazine and β-10-phenothiazinylpropionic acid, with salts, esters, and other derivatives have been prepared as possible anthelmintics. The acid is lethal towards liver fluke (*Fasciola hepatica*) *in vitro*.

THE present paper deals with attempts to prepare improved anthelmintics of the phenothiazine type (I). First, we record that we failed to effect ring-closure, by sulphur, of 2 : 4-dinitro- and 4′-methyl-2 : 4-dinitro-diphenylamine (Reitzenstein, *J. pr. Chem.*, 1903, **68**, 256), 4′-chloro-2 : 4-dinitrodiphenylamine (Reverdin and Crépieux, *Ber.*, 1903, **36**, 33), and 2-amino-4-nitrodiphenylamine and its acetyl derivative (Nietzki and Almenräder, *ibid.*, 1895, **28**, 2971). Although a small amount of hydrogen sulphide was formed when 4-chlorodiphenylamine (Chapman, *J.*, 1929, 569) was heated with sulphur, no chlorophenothiazine could be isolated. Hydrogen bromide was evolved with the 4 : 4′-dibromodiphenylamine, but no hydrogen sulphide could be detected; possibly the sulphur removed the bromine from the compound, which would explain the presence of hydrogen bromide.

Ethyl β-10-phenothiazinylpropionate has been reported by Cauquil and Cassadevall (*Compt. rend.*, 1947, **225**, 578). The alkyl esters were more easily obtained by means of the silver salt of the acid. 10-Phenothiazinylcarbonylmethyl β-10-phenothiazinylpropionate (I) was prepared, since a compound with two phenothiazine residues might have interesting anthelmintic properties. Two arylamides of the acid were also prepared.

(I)  (II) 

Since it has been found that compounds with a keto-methylene group showed anthelmintic activity *in vitro* (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219), 5′ : 6′-dihydro-4′-oxopyridino(3′ : 2′ : 1′-1 : 10*a* : 10)phenothiazine (II) and its benzylidene derivative and semicarbazone were prepared. Baldwin (*ibid.*, 1948, **3**, 91) demonstrated anthelmintic activity *in vitro* for benzylidene derivatives of ketones. The benzylidene derivative did not form a phenylhydrazone.

Although the tests of these compounds against liver fluke (*Fasciola hepatica*) and anterior preparations of the roundworm *Ascaris lumbricoides* will be reported in full elsewhere, it may be mentioned that β-10-phenothiazinylpropionic acid was lethal (1 : 3000) and its sodium salt paralysant (1 : 1000) towards liver fluke.

EXPERIMENTAL

10-Benzoylphenothiazine.—A dry benzene solution (50 c.c.) containing phenothiazine (5 g.) and benzoyl chloride (7 g.) was refluxed for 1 hr. After removal of the benzene, the residue was warmed with aqueous potassium hydroxide (20%; 40 c.c.), and the product filtered off, washed with water, and recrystallised from glacial acetic acid as yellow needles of the benzoylated compound (6 g.), m. p. 177—178° (Found: C, 74·8; H, 4·7. Calc. for $C_{19}H_{13}ONS$: C, 75·3; H, 4·3%). Fraenkel (*Ber.*, 1885, **18**, 1844) gives m. p. 170·5°.

10-(2 : 4-Dichlorobenzoyl)phenothiazine.—A xylene solution (25 c.c.) of freshly distilled

2 : 4-dichlorobenzoyl chloride (6 g.) and phenothiazine (5 g.) was refluxed for 45 min. The xylene was distilled off till the solution became turbid. The crystals obtained on cooling recrystallised from ethanol as colourless prisms of the 2 : 4-*dichlorobenzoyl* derivative (4 g.), m. p. 133—134° (Found : C, 61·5; H, 3·1. $C_{19}H_{11}ONCl_2S$ requires C, 61·3; H, 3·0%).

10-p-*Nitrobenzoylphenothiazine.*—*p*-Nitrobenzoyl chloride (5 g.) was added gradually to an acetic acid solution of phenothiazine (5 g. in 25 c.c.) and the mixture heated for 15 min. Next morning, the product was filtered off and washed in turn with ethanol and acetone. Recrystallisation from xylene afforded bright yellow rectangular plates (3·5 g.), m. p. 225—226°, of the *nitrobenzoyl* derivative (Found : C, 65·9; H, 3·5. $C_{19}H_{12}O_3N_2S$ requires C, 65·5; H, 3·5%).

10-(3 : 5-*Dinitrobenzoyl*)*phenothiazine.*—This *compound* was similarly obtained. Recrystallisation from xylene afforded yellow plates (40% yield), m. p. 265—266° (Found : C, 58·1; H, 2·9. $C_{19}H_{11}O_5N_3S$ requires C, 58·0; H, 2·8%).

10-p-*Anisoylphenothiazine.*—*p*-Anisoyl chloride (9 g.) was added gradually to phenothiazine (10 g.) and pyridine (10 c.c.). A vigorous reaction ensued on warming and the colourless crystals formed on cooling were washed with ethanol and recrystallised from glacial acetic acid. Colourless rectangular prisms of the p-*anisoyl* derivative (13 g.), m. p. 173—174°, were obtained (Found : C, 71·9; H, 4·7. $C_{20}H_{15}O_2NS$ requires C, 72·1; H, 4·2%).

β-10-*Phenothiazinylpropionic Acid.*—This compound was prepared by Smith's method (*J. Org. Chem.*, 1950, **15**, 1125). The sodium salt, obtained by titration, crystallised from absolute ethanol–acetone as colourless needles, m. p. 262—263° (decomp.). The 1-*phenylethylammonium* salt formed colourless needles, m. p. 156—158° (Found : C, 70·5; H, 5·8. $C_{23}H_{24}O_2N_2S$ requires C, 70·4; H, 6·1%), and the S-*benzylthiuronium* salt was obtained as colourless needles, m. p. 160° (both from aqueous ethanol) (Found : C, 63·1; H, 5·2. $C_{23}H_{23}O_2N_3S_2$ requires C, 63·2; H, 5·3%). The *piperazonium* salt crystallised from absolute ethanol as colourless needles, m. p. 190—191° (Found : C, 63·5; H, 5·9. $C_{34}H_{36}O_4N_4S_2,H_2O$ requires C, 63·2; H, 5·9%).

The silver salt of the acid, an alkyl iodide, and sodium-dried benzene were refluxed on the water-bath for 2 hr. After removal of the silver iodide, the filtrate was extracted with aqueous sodium hydrogen carbonate and evaporated. The residue was a red oil which solidified on cooling and was purified by recrystallisation from ethanol (charcoal). The *esters*, except the ethyl ester, are tabulated : all formed colourless needles, except the *iso*propyl (colourless rectangular plates) and the *sec.*-butyl (colourless prisms) ester. The *n*-heptyl ester became greenish-blue in light.

β-10-*Phenothiazinylpropionic esters.*

Ester	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H	M. p.	Yield (%)
Methyl	$C_{16}H_{15}O_2NS$	68·1	5·4	67·4	5·3	64—65°	37
n-Propyl	$C_{18}H_{19}O_2NS$	69·1	6·1	69·0	6·1	34—35	42
*iso*Propyl	$C_{18}H_{19}O_2NS$	69·6	6·4	69·0	6·1	74—75	73
n-Butyl	$C_{19}H_{21}O_2NS$	70·1	6·5	69·7	6·4	85—86	74
*iso*Butyl	$C_{19}H_{21}O_2NS$	69·3	6·4	69·7	6·4	73—74	70
sec.-Butyl	$C_{19}H_{21}O_2NS$	69·5	6·4	69·7	6·4	43—44	80
tert.-Butyl	$C_{19}H_{21}O_2NS$	69·2	6·7	69·7	6·4	76	70
n-Amyl	$C_{20}H_{23}O_2NS$	70·7	6·8	70·4	6·7	74—75	68
n-Hexyl	$C_{21}H_{25}O_2NS$	70·7	7·0	70·9	7·0	52—53	36
n-Heptyl	$C_{22}H_{27}O_2NS$	71·7	7·3	71·6	7·3	46—47	70
n-Octyl	$C_{23}H_{29}O_2NS$	72·2	7·8	72·1	7·6	38—39	70

4-*Nitrobenzyl* β-10-*phenothiazinylpropionate* crystallised from xylene–light petroleum (b. p. 60—80°) in bright yellow needles (55%), m. p. 160—161° (Found : C, 64·2; H, 4·5. $C_{22}H_{18}O_4N_2S$ requires C, 65·0; H, 4·4%).

10-*Phenothiazinylcarbonylmethyl* β-10-*Phenothiazinylpropionate.*—An ethanolic solution of the sodium salt of the acid (2 g.) and 10-chloroacetylphenothiazine (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 107) (2 g.) was refluxed on the water-bath for 3 hr. The product which separated afforded colourless rectangular prisms of the *ester* (1 g.), m. p. 179—180°, from toluene–light petroleum (b. p. 40—60°) (Found : C, 67·9; H, 4·1. $C_{29}H_{22}O_3N_2S_2$ requires C, 68·2; H, 4·3%).

β-10-*Phenothiazinylpropion*-p-*toluidide.*—A xylene solution (15 c.c.) of the acid (4 g.) and *p*-toluidine (8 g.) was refluxed for 3 hr. Benzene (20 c.c.) was added to the cooled product, and the benzene–xylene solution washed in turn with dilute hydrochloric acid, water, aqueous sodium hydroxide, and again water. After drying and removal of the benzene, light petroleum

(b. p. 40—60°) was added to the residue. The *toluidide* which separated recrystallised from benzene–light petroleum (b. p. 40—60°) (charcoal) as colourless matted needles (3 g.), m. p. 140° (Found: C, 72·8; H, 5·6. $C_{22}H_{20}ON_2S$ requires C, 73·3; H, 5·6%).

β-10-*Phenothiazinylpropion*-p-*bromoanilide*.—This *derivative* was prepared similarly from the acid (2 g.). Recrystallisation from absolute ethanol (charcoal) gave colourless needles (1 g.), m. p. 193—194° (Found: Br, 18·2. $C_{21}H_{17}ON_2BrS$ requires Br, 18·8%).

5′-*Benzylidene*-5′ : 6′-*dihydro*-4′-*oxopyridino*(3′ : 2′ : 1′-1 : 10a : 10)*phenothiazine*.—5′ : 6′-Dihydro-4′-oxopyridino(3′ : 2′ : 1′-1 : 10*a* : 10)phenothiazine (Smith, *loc. cit.*) (5 g.), benzaldehyde (5 g.), absolute ethanol (70 c.c.), and 5N-sodium hydroxide (3·5 c.c.) were shaken and set aside for 4 hr.; the precipitated *benzylidene* derivative recrystallised from aqueous methanol in yellow prismatic needles (3·5 g.), m. p. 164° (Found: C, 77·5; H, 5·1. $C_{22}H_{15}ONS$ requires C, 77·4; H, 4·4%).

5′ : 6′-*Dihydro*-4′-*oxopyridino*(3′ : 2′ : 1′-1 : 10a : 10)*phenothiazine Semicarbazone*.—The *semicarbazone* crystallised from chlorobenzene–light petroleum (b. p. 40—60°) as yellow needles, m. p. 237—238° (Found: C, 62·7; H, 4·7; N, 17·6. $C_{16}H_{14}ON_4S$ requires C, 61·9; H, 4·5; N, 18·1%).

The authors are indebted to the Agricultural Research Council for a grant and to Dr. J. W. Minnes for some of the microchemical analyses.

HERIOT-WATT COLLEGE, EDINBURGH. [*Received, March 30th*, 1954.]

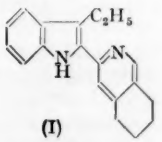
The Constitution of Yohimbine and Related Alkaloids. Part VII. Synthesis of* 5 : 6 : 7 : 8-*Tetrahydroisoquinoline*-3-*carboxylic Acid.*

By R. M. ANDERSON, G. R. CLEMO, and G. A. SWAN.

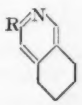
[Reprint Order No. 5270.]

5 : 6 : 7 : 8-Tetrahydro*iso*quinoline-3-carboxylic acid, a degradation product of yohimbine, has been synthesised and converted into 3-acetyl-5 : 6 : 7 : 8-tetrahydro*iso*quinoline.

SELENIUM dehydrogenation of yohimbine gives yobyrine, "tetrahydroyobyrine" (I), and ketoyobyrine (Barger and Scholz, *Helv. Chim. Acta*, 1933, **16**, 1343; Scholz, *ibid.*, 1935, **18**, 923). Ozonolysis of "tetrahydroyobyrine" and subsequent hydrolysis of the intermediate amide yields *o*-aminopropiophenone and 5 : 6 : 7 : 8-tetrahydro*iso*quinoline-3-carboxylic acid (II; R = CO_2H).



(I)



(II)

(III)

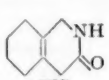
Chuang and Ma (*Ber.*, 1935, **68**, 871), by dehydration of diethyl 1-hydroxy*cyclo*hexane-1 : 2-diacetate obtained a product which may be diethyl *cyclo*hexene-1 : 2-diacetate, the isomer with an exocyclic double bond, or a mixture of the two. Dieckmann cyclisation of this product and subsequent hydrolysis could give either the hitherto undescribed 4 : 5 : 6 : 7-tetrahydroindan-2-one (III), or the isomer with the double bond in the five-membered ring. The latter was synthesised by Islam and Raphael (*J.*, 1952, 4086) and gives a red 2 : 4-dinitrophenylhydrazone, m. p. 200°, whereas our ketone forms a pale orange 2 : 4-dinitrophenylhydrazone, m. p. 183°, and has therefore structure (III). The same ketone is obtained by heating the barium salt of the *cyclo*hexene-1 : 2-diacetic acid.

All attempts to convert the oxime of (III) by the Beckmann reaction into 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-3-oxo*iso*quinoline (IV) failed.

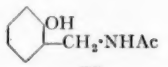
The synthesis of the *iso*quinoline (IV) was investigated by another route. *N*-Acetyl-2-

* Part VI, *J.*, 1952, 650.

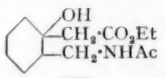
hydroxy*cyclo*hexylmethylamine (V) was oxidised to the corresponding ketone which with ethyl bromoacetate gave ethyl 2-acetamidomethyl-1-hydroxy*cyclo*hexylacetate (VI) which on dehydration and cyclisation gave (IV) or an isomer but the yield was too low for use in the preparation of (II; R = CO_2H).



(IV)



(V)



(VI)

Attempts to prepare the acid (II; R = CO_2H) or its ethyl ester by condensation of 2-aminomethylene*cyclo*hexanone with pyruvic acid or ethyl pyruvate respectively were unsuccessful, starting material being recovered.

It was finally found that 3-chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (Schlittler and Merian, *Helv. Chim. Acta*, 1947, **30**, 1339) could be converted into (II; R = CO_2H) identical with the acid obtained from yohimbine, by treatment with cuprous cyanide in aqueous potassium cyanide.

Whilst 3-chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline did not form a Grignard reagent with magnesium, it formed a lithium derivative which with acetonitrile gave 3-acetyl-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (II; R = Ac) in low yield. Claisen condensation of the ester (II; R = CO_2Et) with ethyl acetate and subsequent hydrolysis afforded a better yield of the ketone.

Experimental

Ultra-violet absorption measurements were made in ethanol with a Hilger "Uvispec" spectrophotometer.

4 : 5 : 6 : 7-*Tetrahydroindan*-2-*one* (III).—Diethyl *cyclo*hexene-1 : 2-diacetate (6·0 g.) was added slowly to a suspension of sodium ethoxide (from sodium, 1·4 g.) in dry benzene (50 ml.), and the mixture was refluxed for 12 hr. The dark red mixture was cooled, concentrated hydrochloric acid (100 ml.) added, and the whole refluxed for 12 hr. After dilution with water, the aqueous layer was separated and extracted with ether, and the extract washed with dilute sodium hydroxide and then water and dried (Na_2SO_4). Distillation afforded the crude ketone (1·3 g.) as a pale yellow oil, b. p. 98—105°/2 mm. The *semicarbazone* separated from aqueous ethanol in colourless needles, m. p. 231—232° (Found: C, 62·4; H, 8·1. $C_{10}H_{15}ON_3$ requires C, 62·2; H, 7·8%), and on hydrolysis by aqueous oxalic acid gave the pure *ketone*, a colourless oil, b. p. 110°/3 mm. (Found: C, 79·3; H, 9·1. $C_9H_{12}O$ requires C, 79·4; H, 8·8%). The 2 : 4-*dinitrophenylhydrazone* formed pale orange needles (from ethanol), m. p. 183° (Found: C, 57·0; H, 5·4. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1%); light absorption: max. at 2700 and 3880 Å (log ε 3·86 and 4·12 respectively); min. at 3160 Å (log ε 2·70). The *oxime* crystallised from aqueous ethanol in almost colourless needles, m. p. 108—110° (decomp.) (Found: C, 71·0; H, 8·9. $C_9H_{13}ON$ requires C, 71·5; H, 8·6%).

N-*Acetyl*-2-*hydroxy*cyclo*hexylmethylamine* (V).—A suspension of 2-hydroxy*cyclo*hexyl-1-methylamine (cf. Godchot and Mousseron, *Compt. rend.*, 1933, **196**, 621) (2·0 g.) in water (10 ml.) was shaken 2 hr. at room temperature with acetic anhydride (0·887 ml.), the solution extracted with chloroform, the extract dried (Na_2SO_4), and the chloroform removed, yielding the N-*acetyl* derivative (0·84 g.) as a gum which solidified on cooling and crystallised from benzene in small, colourless prisms, m. p. 108—109° (Found: C, 63·2; H, 10·1. $C_9H_{17}O_2N$ requires C, 63·2; H, 9·9%).

N-*Acetyl*-2-*oxo*cyclo*hexylmethylamine*.—A solution of the hydroxyamine (V) (5·0 g.) in acetic acid (22 ml.) was cooled in ice and chromic anhydride (2·4 g.) in water (8 ml.) and acetic acid (32 ml.) was added dropwise with stirring at 0°. The whole was kept for a further 3 hr. at 0°, then at room temperature overnight, and at 40—50° for 1 hr. The solvents were removed under reduced pressure at 50—60°, and the residue was dissolved in warm methanol (4 ml.) and shaken vigorously with ether (100 ml.). The ether solution was decanted from the chromium salts, the residue was extracted with ether, and the combined ether extracts were boiled to coagulate chromium salts, and filtered. Distillation gave the *ketone* (2·9 g.) as a colourless, viscous oil, b. p. 146—149°/2 mm. (Found: C, 63·7; H, 9·2. $C_9H_{15}O_2N$ requires C, 63·9; H, 8·9%). The *semicarbazone* separated from water in almost colourless prisms, m. p. 214—215° (Found: C, 53·3; H, 7·9. $C_{10}H_{18}O_2N_4$ requires C, 53·1; H, 8·0%).

Ethyl 2-*Acetamidomethyl*-1-*hydroxy*cyclo*hexylacetate* (VI).—A mixture of the above ketone

(5 g.), ethyl bromoacetate (5·4 g.), anhydrous benzene (20 ml.), freshly cleaned zinc wool (2·9 g.), and a trace of iodine was stirred and heated under reflux on the water-bath for 2 hr. The mixture was cooled, sufficient 10% sulphuric acid added to dissolve residual zinc, the benzene layer separated, and the aqueous layer extracted with ether. The ether extract was washed with dilute sodium hydrogen carbonate solution, then with water, and dried (Na_2SO_4). Distillation gave a pale yellow, viscous oil (1·7 g.), b. p. 160—165°/0·2 mm., which solidified on the addition of dry ether. Recrystallisation from dry ether gave the *ester* as colourless prisms, m. p. 75° (Found: C, 60·3; H, 9·1. $C_{13}H_{23}O_4N$ requires C, 60·7; H, 9·0%).

Dehydration of the Ester (VI).—The above ester (0·7 g.) was dissolved in benzene (5 ml.), freshly distilled pyridine (0·85 ml.) was added, and the mixture cooled in ice. Freshly distilled thionyl chloride (0·23 ml.) was added dropwise, below 5°. The mixture was kept at room temperature overnight, then poured with stirring on crushed ice, and the benzene layer separated. The aqueous layer was extracted with benzene. The combined benzene extracts were washed with dilute hydrochloric acid, then with dilute sodium carbonate solution, and finally with water, and dried (Na_2SO_4). Distillation gave a pale yellow, viscous oil (0·4 g.), b. p. 145—150°/0·2 mm. (Found: C, 65·6; H, 9·0. Calc. for $C_{13}H_{21}O_3N$: C, 65·3; H, 8·8%).

Cyclisation of the Dehydration Product.—The above product (0·2 g.) was refluxed with 10% ethanolic potassium hydroxide (2 ml.) for 2·5 hr. The ethanol was removed under reduced pressure and the residue dissolved in a little water, cooled in ice, and treated with excess of 10% sulphuric acid. A slight excess of sodium carbonate was then added, the solution evaporated to dryness under reduced pressure, and the residue extracted with boiling anhydrous benzene. The benzene extract was filtered, and the benzene removed, giving the *iso*quinolone (IV or its isomer) as a white solid (10 mg.) which crystallised from anhydrous benzene in colourless, rectangular plates, m. p. (Kofler block) 135—138° (Found: C, 71·4; H, 8·9. Calc. for $C_9H_{13}ON$: C, 71·5; H, 8·6%), and gave a red colour with ethanolic ferric chloride.

5 : 6 : 7 : 8-*Tetrahydro*isoquinoline-3-carboxylic Acid.—3-Chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline formed a *picrate* (yellow needles from ethanol), m. p. 103—105° (Found: C, 45·2; H, 3·6. $C_9H_{10}NCl,C_6H_3O_7N_3$ requires C, 45·4; H, 3·3%).

The above chloro-base (1 g.) in ethanol (1 ml.) was added to freshly prepared cuprous cyanide (0·6 g.) in potassium cyanide (1·5 g.) and water (5 ml.). The mixture was heated at 180—190° for 10 hr., cooled, and filtered. The pH of the filtrate was adjusted to 4, the precipitated cuprous salts were filtered off, and the clear yellow filtrate was continuously extracted with ether for 48 hr. Removal of the ether from the dried (Na_2SO_4) extract gave the *acid* (0·19 g.) which separated from water in colourless needles, m. p. 209—210° (Found: C, 67·7; H, 6·4. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2%). Light absorption: max. at 2250 and 2660 Å (log ε 3·83 and 3·50); min. at 2500 Å (log. ε 3·40).

The acid (II; R = CO_2H) from yohimbine had m. p. 208°, mixed m. p. with our synthetic acid 208—209°, and light absorption max. at 2260 and 2660 Å (log ε 3·80 and 3·50 respectively), min. at 2510 Å (log ε 3·38).

The synthetic acid (0·3 g.) in anhydrous ethanol (15 ml.) was saturated at 0° with dry hydrogen chloride, gently warmed for 2 hr., refluxed for 2 hr., and kept at room temperature overnight. Removal of the ethanol in a vacuum and working up as usual gave the *ester* (0·2 g.), b. p. 115°/2 mm. (Found: C, 70·4; H, 7·5. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3%). The *picrate* crystallised from methanol in yellow plates, m. p. 150—151° (Found: C, 50·0; H, 4·4. $C_{12}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 49·8; H, 4·15%).

3-*Acetyl*-5 : 6 : 7 : 8-*tetrahydro*isoquinoline.—To a suspension of potassium ethoxide (from potassium, 0·2 g.) in dry benzene (8 ml.) was added the above ester (0·2 g.) and ethyl acetate (0·5 g., 2 mols.) The mixture immediately became brown and was refluxed for 5 hr., cooled, treated with hydrochloric acid (2 : 1; 10 ml.), and heated under reflux on the water-bath for a further 12 hr. It was evaporated to dryness in a vacuum, and the residue was dissolved in water, basified with saturated K_2CO_3, and extracted with ether. Distillation of the dried (K_2CO_3) extract gave the ketone (0·1 g.) as a pale yellow, viscous oil, b. p. (bath-temp.) 150°/2 mm. The *picrate* separated from ethanol in yellow plates, m. p. 146—147° (decomp.) (Found: C, 50·3; H, 4·2. $C_{11}H_{13}ON,C_6H_3O_7N_3$ requires C, 50·5; H, 4·0%).

We thank Professor M.-M. Janot for a gift of 5 : 6 : 7 : 8-tetrahydro*iso*quinoline-3-carboxylic acid of natural origin, and one of us (R. M. A.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, April 1st,* 1954.]

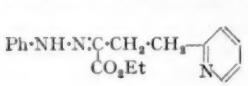
Syntheses in the Indole Series.

By G. R. Clemo and J. C. Seaton.

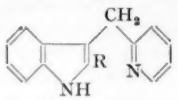
[Reprint Order No. 5279.]

3-(2-Pyridylmethyl)indole (II; R = H) and 3-indolyl 2-pyridyl ketone (III) have been prepared, and an attempt made to cyclise them by the Scholl and other methods to give the tetracyclic system of lysergic acid. A rearrangement of some 3-substituted indoles to the corresponding 2-substituted compounds has been noted.

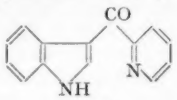
3-(2-Pyridylmethyl)indole (II) was prepared by condensing benzenediazonium chloride with ethyl β-(2-pyridylethyl)acetoacetate (cf. Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2461) in alkaline solution to give the hydrazone (I), cyclisation by alcoholic hydrogen chloride, and hydrolysis and decarboxylation of the resulting ester (II; R = CO_2Et). When 3-(2-pyridylmethyl)indole-2-carboxylic acid (II; R = CO_2H) was heated, water was eliminated and 4-oxoindolo(3′ : 2′-2 : 3)pyridocoline (IV) was obtained.



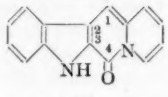
(I)



(II)



(III)



(IV)

Attempts to cyclise the base (II; R = H) by hot aluminium chloride–sodium chloride, however, isomerised it. In order to elucidate this, 3-benzylindole was prepared (cf. Robinson, Cornforth, and West, U.S.P. 2,407,452/1946) and heated with aluminium chloride–sodium chloride; it gave 2-benzylindole (Julian and Pikl, *J. Amer. Chem. Soc.*, 1933, **55**, 2105). Similarly skatole rearranged to 2-methylindole and it was therefore concluded that the pyridyl isomer was 2-(2-pyridylmethyl)indole. This appears to be the first record of such isomerisation in the indole series.

When however 3-benzylindole and 3-(2-pyridylmethyl)indole were *N*-acetylated by means of the indole Grignard reagent no such rearrangement occurred on fusion with aluminium chloride–sodium chloride. The former gave a product from which a small amount of anthracene was isolated.

With selenium dioxide the base (II; R = H) gave 3-indolyl 2-pyridyl ketone (III), but when this was heated with aluminium chloride and sodium chloride only the starting material was recovered.

2 : 5-Dichlorobenzenediazonium chloride coupled with ethyl β-(2-pyridylethyl)acetoacetate to give the 2 : 5-dichlorophenylhydrazone corresponding to (I). When this was regenerated from acid solution the product had a different melting point and it is suggested that this hydrazone can exist in stable *syn*- and *anti*-forms. The hydrazone did not cyclise when heated in alcohol and sulphuric acid at 180° or in alcohol with zinc chloride at 125°, but at 150° 4′ : 7′-dichloro-4-oxoindolo(3′ : 2′-2 : 3)pyridocoline was formed.

Experimental

Ethyl α-Phenylhydrazono-γ-2-pyridylbutyrate Hydrochloride (*as* I).—Ethyl β-(2-pyridylethyl)-acetoacetate (36 g.) in ethanol (100 ml.) was cooled in ice, while a solution of sodium hydroxide (30 g.) in water (80 ml.) was added, followed at once by one of benzenediazonium chloride prepared from aniline (16 g.) in concentrated hydrochloric acid (80 ml.). A dark reddish-brown oil was liberated. After several minutes water was added and the oil extracted with ether. After removal of the solvent, hydrochloric acid was added to the residue, and the whole again evaporated to dryness; the crystalline *hydrochloride* remained. Crystallisation twice from alcohol gave straw-coloured plates (32 g.), m. p. 195° (Found : C, 61·2; H, 6·2, $C_{17}H_{19}O_2N_3,HCl$ requires C, 61·2; H, 6·0%).

Ethyl 3-(2-Pyridylmethyl)indole-2-carboxylate (II; R = CO_2Et).—A solution of the above hydrazone (20 g.) in absolute ethanol (200 ml.) was saturated with dry hydrogen chloride and refluxed for 3 hr. The alcohol was removed, and the residue was dissolved in water and basified

with sodium carbonate. The ester that separated soon solidified and was filtered off and recrystallised from benzene to give buff-coloured needles (9·6 g.), m. p. 129° (Found: C, 72·8; H, 6·0. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·7%).

3-(2-*Pyridylmethyl*)*indole*-2-*carboxylic Acid* (II; R = CO_2H).—The ester was refluxed with sodium hydroxide (5 g.) in methanol (30 ml.) for 6 hr. Water was added and the methanol removed. The pH was adjusted to 7 with dilute hydrochloric acid, and the solution extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed, leaving a white *acid* which, recrystallised from benzene (6 g.), had m. p. 135° (Found: C, 71·4; H, 4·9. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

3-(2-*Pyridylmethyl*)*indole* (II; R = H).—The acid (6 g.) was boiled with concentrated hydrochloric acid for 1 hr. The solution was basified with sodium carbonate and extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed, leaving the *base* as a brown gum, which separated from light petroleum (b. p. 60—80°) (charcoal) in colourless prisms (4·1 g.), m. p. 104° (Found: C, 80·9; H, 6·0; N, 13·4. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·4%). A pink colour was obtained with Ehrlich's reagent on heating. The *monopicrate* crystallised from ethanol in fine yellow needles, m. p. 121° (Found: C, 54·55; H, 4·1. $C_{14}H_{12}N_2,C_6H_3O_7N_3,C_2H_5{\cdot}OH$ requires C, 54·65; H, 4·35%).

4-*Oxoindolo*(3′ : 2′-2 : 3)*pyridocoline* (IV).—The carboxylic acid (0·5 g.) was heated at 200°/0·1 mm. Yellow crystals of the *indolopyridocoline* sublimed. Recrystallisation from benzene gave yellow needles, m. p. 308° (Found: C, 76·4; H, 4·6. $C_{15}H_{10}ON_2$ requires C, 76·9; H, 4·3%).

2-(2-*Pyridylmethyl*)*indole*.—The base (II; R = H) (0·6 g.) was heated with anhydrous aluminium chloride (0·6 g.) and sodium chloride (0·05 g.) at 250° for 30 min. The melt was decomposed with ice and hydrochloric acid, basified, and extracted with ether. The extract was dried (Na_2SO_4) and the ether removed giving a brown gum, which was extracted with boiling light petroleum (b. p. 60—80°). The concentrated extract was treated with charcoal and on cooling, fine colourless needles of the *isomer* were obtained (0·2 g.), having m. p. 96° (Found: C, 80·8; H, 5·6%). A transient pink colour was obtained with Ehrlich's reagent. The *monopicrate* crystallised from ethanol in stout yellow solvated prisms, m. p. 183° (Found: C, 54·55; H, 4·4%).

2-*Benzylindole*.—3-Benzylindole (1 g.) was heated with anhydrous aluminium chloride (1 g.) and sodium chloride (0·1 g.) at 240° for 20 min. The melt was treated as above. The dark oil from the ether extract was distilled (air-bath temp., 150°/0·1 mm.). The colourless distillate solidified and, crystallised from light petroleum (b. p. 60—80°) (0·63 g.), had m. p. 84°, not depressed on admixture with an authentic specimen (Julian and Pikl, *loc. cit.*) (Found: C, 87·0; H, 6·4. Calc. for $C_{15}H_{13}N$: C, 86·95; H, 6·3%). The picrate crystallised from light petroleum (b. p. 60—80°) in red needles, m. p. 115°.

2-*Methylindole*.—3-Methylindole (1 g.) was heated with anhydrous aluminium chloride (1 g.) and sodium chloride (0·1 g.) at 250° for 20 min. The melt was treated as above. The residue from the ether was distilled (b. p. 120°/3 mm.) and, crystallised from light petroleum (b. p. 60—80°) (0·36 g.), 2-methylindole had m. p. and mixed m. p. 59°.

1-*Acetyl*-3-*benzylindole*.—A Grignard reagent prepared from magnesium (0·25 g.) and methyl iodide (2·7 g.) in dry ether (10 ml.) was cooled in ice, and a solution of 3-benzylindole (2 g.) in dry ether (20 ml.) was added slowly. The mixture was kept for 1 hr. and then refluxed for 30 min. A solution of acetyl chloride (0·5 g.) in ether (10 ml.) was added slowly to the cooled mixture which was set aside and then refluxed for 30 min. It was cooled, aqueous ammonium chloride was added, and the ether layer was separated, dried (Na_2SO_4), and evaporated. The residual *acetyl* derivative crystallised from light petroleum (b. p. 60—80°) in large colourless prisms (1·7 g.), m. p. 71° (Found: C, 81·9; H, 6·4. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·0%).

1-*Acetyl*-3-(2-*pyridylmethyl*)*indole*.—A Grignard reagent was prepared by warming magnesium (0·5 g.) and ethyl iodide (2·2 g.) in dry benzene (15 ml.) and ether (1 ml.) at 70° for 3 hr. Dry benzene (50 ml.) and then a solution of 3-(2-pyridylmethyl)indole (1 g.) in benzene (20 ml.) were added in 30 min. to the boiling mixture. After 1 hour's refluxing ethyl acetate (2 g.) was added and heating continued for 3 hr. The solution was cooled and aqueous ammonium chloride added. The benzene layer was evaporated, leaving a brown oil, which was separated in benzene solution on an alumina column into 1-*acetyl*-3-(2-*pyridylmethyl*)*indole*, crystallising from light petroleum (b. p. 60—80°) in colourless prisms (0·3 g.), m. p. 52° (Found: C, 76·6; H, 5·9. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%), and 3-(2-pyridylmethyl)indole (0·5 g.), m. p. 104°. The yellow *methiodide* of the acetylindole had m. p. 263° (Found: C, 51·8; H, 4·5. $C_{16}H_{14}ON_2,CH_3I$ requires C, 51·8; H, 4·3%).

Action of Aluminium Chloride–Sodium Chloride on 1-*Acetyl*-3-*benzylindole*.—The acetylindole (1 g.) was heated with anhydrous aluminium chloride (1 g.) and sodium chloride at 150° for 45 min. The melt was decomposed, and evaporation of its ether extract gave a brown oil, which when passed down an alumina column in benzene yielded a band from which plates crystallising from ethanol were obtained (1 mg.), m. p. 204—208° not depressed on admixture with anthracene. The ultra-violet absorption spectrum was also identical with that of anthracene. Nothing further was eluted with benzene, but chloroform eluted a thick brown gum (0·05 g.) which did not crystallise.

Action of Aluminium Chloride–Sodium Chloride on 1-*Acetyl*-3-(2-*pyridylmethyl*)*indole*.—The acetylindole (1 g.), when heated as above with aluminium chloride (1 g.) and sodium chloride (0·1 g.) at 150° for 30 min., yielded 1-acetyl-3-(2-pyridylmethyl)indole (0·2 g.) and the base (II; R = H) (0·2 g.).

3-*Indolyl* 2-*Pyridyl Ketone* (III).—The base (II; R = H) (2 g.) was refluxed with selenium dioxide (2 g.) in dioxan (30 ml.) for 1¼ hr. The dark solution was filtered and the dioxan removed, giving a dark red residue which was extracted several times with boiling benzene. The extracts were treated with charcoal and concentrated, to give the crystalline *ketone*, which crystallised from benzene in cream-coloured prisms (0·5 g.), m. p. 191° (Found: C, 75·8; H, 4·7. $C_{14}H_{10}ON_2$ requires C, 75·65; H, 4·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in deep red prisms, m. p. 293—295° (Found: C, 59·4; H, 3·5. $C_{20}H_{14}O_4N_6$ requires C, 59·7; H, 3·5%).

When the ketone (0·5 g.) was heated with anhydrous aluminium chloride (0·5 g.) and sodium chloride (0·05 g.) at 250° for 1 hr., and the melt was decomposed and extracted as above, only unchanged ketone (4 mg.) was recovered.

Ethyl α-2 : 5-*Dichlorophenylhydrazono*-γ-2′-*pyridylbutyrate*.—Ethyl β-(2-pyridylethyl)acetoacetate (4 g.) in ethanol (20 ml.) was cooled in ice while a solution of sodium hydroxide (4 g.) in water (10 ml.) was added, followed by one of 2 : 5-dichlorobenzenediazonium chloride prepared from 2 : 5-dichloroaniline (3 g.) and hydrochloric acid (90 ml.; 1 : 5). After a few minutes water was added and the dark oil extracted with ether. The extract was dried (Na_2SO_4) and the ether removed, giving the *hydrazone* which crystallised from ethanol in straw-coloured needles (3·3 g.), m. p. 101° (Found: C, 55·8; H, 4·8; N, 11·8. $C_{17}H_{17}O_2N_3Cl_2$ requires C, 55·7; H, 4·65; N, 11·5%). The *hydrochloride* crystallised from ethanol in straw-coloured prisms, m. p. 178—180° (Found: C, 50·65; H, 4·7. $C_{17}H_{17}O_2N_3Cl_2$,HCl requires C, 50·7; H, 4·5%). Regeneration of the hydrazone gave pale yellow prisms (m. p. 62°) crystallising from ethanol (Found: C, 56·1; H, 4·8; N, 11·3%).

4′ : 7′-*Dichloro*-4-*oxoindolo*(3′ : 2′-2 : 3)*pyridocoline*.—The dichlorohydrazone (0·5 g.) was heated with zinc chloride (2·5 g.) in dry ethanol (5 ml.) at 150° for 8 hr.; the mixture was evaporated to small bulk, basified, and extracted with chloroform. From the extract yellow needles (0·1 g.), m. p. 327° (from benzene or ethanol), of the *indolopyridocoline* were obtained (Found: C, 59·0; H, 2·7. $C_{15}H_8ON_2Cl_2$ requires C, 59·4; H, 2·6%).

One of us (J. C. S.) thanks the D.S.I.R. for a maintenance grant.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, April* 3*rd*, 1954.]

Griseofulvin. Part IX. Isolation of the Bromo-analogue from* Penicillium griseofulvum *and* Penicillium nigricans.

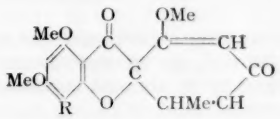
By J. MacMillan.

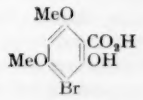
[Reprint Order No. 5285.]

7-Bromo-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione, the bromo-analogue of griseofulvin, has been isolated from the culture filtrates of both *Penicillium griseofulvum* Dierckx and *Penicillium nigricans* (Bainier) Thom, grown on a synthetic medium containing potassium bromide.

When grown on a Czapek–Dox medium, *Penicillium griseofulvum* Dierckx and *P. nigricans* (Bainier) Thom (formerly known as *P. janczewskii* Zal.) produce griseofulvin (I; R = Cl) (Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240; Brian, Curtis, and Hemming, *Trans. Brit. Mycol. Soc.*, 1949, **32**, 30). The former mould and some strains of the latter also produce dechlorogriseofulvin (I; R = H) under the same conditions (MacMillan, *J.*, 1953, 1697). The bromo-analogue (I; R = Br) has now been isolated from the culture filtrates of these fungi grown on a Czapek–Dox medium in which the potassium chloride was replaced by an equivalent amount of potassium bromide.

(I)





(II)

The new metabolic product, $C_{17}H_{17}O_6Br$, was assigned the structure (I; R = Br) by analogy with griseofulvin (Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977) which it closely resembles in its ultra-violet and infra-red light absorption. Like griseofulvin, it gave 3-methoxy-2 : 5-toluquinone on oxidation with chromic oxide while the substitution pattern of the aromatic ring was confirmed by permanganate oxidation to 3-bromo-2-hydroxy-4 : 6-dimethoxybenzoic acid (II) whose structure was proved by synthesis as follows.

2-Bromo- and 2 : 6-dibromo-3 : 5-dimethoxyphenol were prepared in an unambiguous manner from methyl 4-hydroxy-2 : 6-dimethoxybenzoate by bromination followed by hydrolysis and decarboxylation (cf. Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967). They were also obtained on a preparative scale by direct bromination of 3 : 5-dimethoxyphenol. Treatment of the 2-bromo-derivative with chloroacetyl chloride and ring closure of the resulting 3-bromo-ω-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone yielded 7-bromo-4 : 6-dimethoxycoumaranone from which the required acid (II) was obtained by oxidation.

7-Bromo-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = Br) is the first bromine-containing mould metabolite to be isolated although Clutterbuck, Mukhopadhyay, Oxford, and Raistrick (*Biochem. J.*, 1940, **34**, 664) have demonstrated the ability of *Caldariomyces fumago* Woronichin, strain Ag 92, to convert 40% of the supplied inorganic bromide into an unidentified organic form.

The bromo-compound (I; R = Br) produces a typical griseofulvin-like response into *Botrytis allii* (Brian, *Ann. Bot.*, 1949, **13**, 59). The minimum concentration causing an obvious response is 0·75 μg./ml. compared with 0·1 and 6·25 μg./ml. for griseofulvin and dechlorogriseofulvin respectively.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney. In chromatography B.D.H. alumina was rendered alkali-free (Prins and Shoppee, *J.*, 1946, 498) and activated for 3 hr. at 250°/15 mm.

Isolation of 7-Bromo-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione.—The strain of *P.*

* Part VIII, *J.*, 1954, 429.

griseofulvum used in this work (our No. 374) was obtained from Professor Raistrick (L.S.H.T.M. catalogue No. P38) in 1948. The strain (No. 250) of *P. nigricans* which was used produces griseofulvin but not dechlorogriseofulvin on Czapek–Dox medium (MacMillan, *loc. cit.*).

The fungi were cultured by P. J. Curtis, G. L. F. Norris, and G. C. Pick of these laboratories as follows. The Czapek–Dox medium (7·5% glucose) was modified by replacing the potassium chloride by an equivalent amount of potassium bromide; it was made up by dissolving the " AnalaR " glucose in glass-distilled water and passing this solution through a column of B.D.H. " De-acidite F " before adding the " AnalaR " inorganic salts. The medium was dispensed in 1000 ml. portions in earthenware vessels and incubated at 25° for 18—24 days after inoculation. The liquid medium was then separated from the mycelium by filtration and was extracted with chloroform.

(*a*) The brown gum (1·4 g.), obtained from the culture filtrates (24 l.) of *P. nigricans* after 24 days' incubation, was dissolved in benzene (15 ml.), and the solution, after extraction with sodium carbonate, was passed through a column of alumina (7 × 1·5 cm.). Elution with benzene in ultra-violet light gave (i) a colourless band with bright blue fluorescence, recovery yielding an oil (140 mg.) which was retained, and (ii) a pale brown band fluorescing blue; fractional crystallisation of the solid recovered from (ii), from methanol, afforded 7-*bromo*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = Br) (62 mg.), m. p. 204—205°, and dechlorogriseofulvin (73 mg.), m. p. and mixed m. p. 179—181°.

From the second half of this batch which was harvested after only 18 days' incubation, the bromo-compound (I; R = Br) (21 mg.) and dechlorogriseofulvin (40 mg.) were obtained from 24 l. of culture filtrate.

(*b*) The brown gum, obtained from the culture filtrates (48 l.) of *P. griseofulvum* after 20 days' incubation, was crystallised from methanol (25 ml.), giving crude dechlorogriseofulvin (3·2 g.) and filtrate A. The former after chromatography on alumina crystallised from methanol in needles (2·6 g.), m. p. and mixed m. p. 179—181°.

The gum recovered from filtrate A was separated into a light petroleum (b. p. 60—80°)-soluble oil, which was retained, and an insoluble fraction, a solution of which in ethyl acetate was extracted in turn with sodium hydrogen carbonate and sodium hydroxide (acidification of these extracts yielded intractable gums). The neutral gum, obtained by evaporation of the ethyl acetate layer, crystallised from methanol, giving dechlorogriseofulvin (0·8 g.), m. p. 176—179°; the gum from the mother-liquors in benzene (15 ml.) was chromatographed on alumina (10 × 1 cm.), and the band fluorescing blue in ultra-violet light was eluted with benzene. Fractional crystallisation of the recovered solid from methanol gave the bromo-compound (I; R = Br) (67 mg.), m. p. 204—205°, and dechlorogriseofulvin (50 mg.), m. p. 178—180°.

7-Bromo-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione crystallised from benzene or methanol in needles, m. p. 204—205° (Found : C, 51·4, 51·3; H, 4·5, 4·45; Br, 19·7; OMe, 23·3. $C_{17}H_{17}O_6Br$ requires C, 51·4; H, 4·3; Br, 20·1; 3OMe, 23·4%). Light absorption in ethanol : Max. ~325, 292, ~255, 235 (log ε, 3·75, 4·365, 4·22, 4·38). The infra-red spectrum, determined on a Nujol mull, showed absorption max. at 1703, 1653, 1613, and 1577 cm.$^{-1}$ in the double-bond stretching regions. The bromo-compound gave a pale yellow colour with concentrated nitric acid at room temperature.

Oxidation of 7-*Bromo*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione*.—(a) *Chromic oxide*. The bromo-compound (35 mg.) in warm acetic acid (0·5 ml.) was oxidised with chromic oxide (100 mg.) in acetic acid (0·5 ml.) and water (0·2 ml.), as described for griseofulvin (Grove *et al.*, *J.*, 1952, 3967) giving 3-methoxy-2 : 5-toluquinone, m. p. and mixed m. p. 147—149°.

(b) *Potassium permanganate*. To the bromo-compound (94 mg.) in acetone (25 ml.) at room temperature, powdered potassium permanganate (380 mg.) was added in portions (3 hr.) with occasional shaking. The brown precipitate was collected after 15 hr. and was extracted with dilute aqueous ammonia (3 × 2·5 ml.); acidification and recovery gave 3-bromo-2-hydroxy-4 : 6-dimethoxybenzoic acid (3 mg.) which crystallised from acetic acid in needles, m. p. 225—227° (decomp.), and was identical (mixed m. p. and infra-red spectrum) with the synthetic specimen described below.

Bromination of Methyl 4-*Hydroxy*-2 : 6-*dimethoxybenzoate*.—(*a*) The ester (140 mg.) (Pfeffer and Fischer, *Annalen*, 1912, **389**, 207) in chloroform (60 ml.) was treated with bromine (106 mg.) in chloroform (1 ml.) and set aside for 48 hr. After being washed with water, the dried chloroform solution was concentrated and the resulting solid was fractionally crystallised from benzene, yielding (i) the 3-*bromo*-derivative, needles (100 mg.), m. p. 158—159° (Found : C, 41·6; H, 3·9; Br, 27·15. $C_{10}H_{11}O_5Br$ requires C, 41·3; H, 3·8; Br, 27·45%), and (ii) the 3 : 5-*dibromo*-derivative which, after sublimation at 60°/10^{-4} mm., crystallised from light petroleum (b. p.

40—60°) in needles (15 mg.), m. p. 82—83° depressed below 60° on admixture with 2-bromo-3 : 5-dimethoxyphenol, m. p. 79—81° (Found: C, 32·7; H, 2·85. $C_{10}H_{10}O_5Br_2$ requires C, 32·45; H, 2·7%). The infra-red spectrum of the 2 : 6-dibromo-compound showed carbonyl and hydroxyl absorption at 1725 and 3400 cm.$^{-1}$ respectively.

(*b*) Bromine (755 mg.) in acetic acid (5 ml.) was added to the ester (1·0 g.) in acetic acid (150 ml.) and, after 24 hr., the solvent was removed. Fractional crystallisation of the residual gum from benzene gave the 3-bromo-derivative (750 mg.), m. p. 158—159°, and 2 : 6-*dibromo*-3 : 5-*dimethoxyphenol* (150 mg.), m. p. 164—165° (Found: C, 30·6; H, 2·9; Br, 51·1. $C_8H_8O_3Br_2$ requires C, 30·8; H, 2·6; Br, 51·2%).

2-*Bromo*-3 : 5-*dimethoxyphenol*.—Methyl 3-bromo-4-hydroxy-2 : 6-dimethoxybenzoate (100 mg.) in concentrated sulphuric acid (0·3 ml.) was set aside for 1 hr. at 18° and was then poured over crushed ice. The precipitated solid A was collected and the filtrate, after several days, deposited 2-bromo-3 : 5-dimethoxyphenol which was sublimed at 60°/10^{-3} mm. and crystallised from light petroleum in needles, m. p. 78—80°, identical (mixed m. p. and infra-red spectrum) with the monobromo-compound obtained as below by bromination of 3 : 5-dimethoxyphenol.

The solid A consisted of starting material (m. p. and mixed m. p. 154—156°) and a fraction, m. p. 45—90°, soluble in sodium hydrogen carbonate solution.

Bromination of 3 : 5-*Dimethoxyphenol*.—Bromine (7·0 g.) in chloroform (15 ml.) was added slowly and with shaking to the phenol (6·7 g.) in chloroform (15 ml.) at room temperature. After 48 hr., the solvent was removed and the residual gum was distilled at 103°/0·3 mm., giving the 2-*bromo*-derivative (6·0 g.), needles, m. p. 79—81°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 41·1; H, 4·2; Br, 34·4. $C_8H_9O_3Br$ requires C, 41·2; H, 3·9; Br, 34·3%); the *acetate* crystallised from methanol in plates, m. p. 92—93° (Found: C, 43·7; H, 4·3; Br, 29·2. $C_{10}H_{11}O_4Br$ requires C, 43·65; H, 4·0; Br, 29·6%).

Sublimation of the residue from the distillation of the 2-bromo-compound yielded the 2 : 6-dibromo-derivative which crystallised from benzene in needles (1·1 g.), m. p. 165—167°, identical (m. p. and mixed m. p.) with the dibromo-compound obtained in the bromination of methyl 4-hydroxy-2 : 6-dimethoxybenzoate (Found: C, 30·7; H, 2·8; Br, 51·4%); the *acetate* crystallised from methanol in prisms, m. p. 152—153° (Found: C, 34·2; H, 3·0; Br, 45·1. $C_{10}H_{10}O_4Br_2$ requires C, 33·9; H, 2·9; Br, 45·2%).

3-*Bromo*-ω-*chloro*-2-*hydroxy*-4 : 6-*dimethoxyacetophenone*.—2-Bromo-3 : 5-dimethoxyphenol (1·0 g.), chloroacetyl chloride (0·9 g.), nitrobenzene (1·5 g.), and aluminium chloride (1·4 g.) were allowed to stand at 18° for 4 days. After the addition of ice-water (20 ml.) and concentrated hydrochloric acid (4 ml.), the nitrobenzene was removed by steam-distillation; the *acetophenone* which separated as a gummy solid on cooling crystallised from dioxan in pale yellow needles (25% yield), m. p. 211—213° [Found: C, 38·8; H, 3·4; Hal. (calc. as Cl), 26·4. $C_{10}H_{10}O_4BrCl$ requires C, 38·8; H, 3·3; Hal., 26·45%].

7-*Bromo*-4 : 6-*dimethoxycoumaran*-3-*one*.—The above ω-chloroacetophenone (350 mg.) was heated under reflux for 2·5 hr. with methanol (40 ml.) and crystalline sodium acetate (500 mg.). The *coumaranone*, which separated on cooling, crystallised from dioxan in needles (265 mg.), m. p. 219—221° (decomp.) (Found: C, 43·9; H, 3·7; Br, 29·4. $C_{10}H_9O_4Br$ requires C, 44·0; H, 3·3; Br, 29·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene–methanol in crimson needles, m. p. 236° (decomp.) (Found: C, 42·9; H, 2·8; N, 12·4. $C_{16}H_{13}O_7N_4Br$ requires C, 42·4; H, 2·9; N, 12·4%).

3-*Bromo*-2-*hydroxy*-4 : 6-*dimethoxybenzoic Acid*.—The foregoing coumaranone (220 mg.) in acetone (40 ml.) was treated with potassium permanganate (500 mg.) in acetone (20 ml.), and the mixture was set aside for 2 days. Extraction of the brown precipitate with dilute ammonia solution (25 ml.) and acidification gave 3-*bromo*-2-*hydroxy*-4 : 6-*dimethoxybenzoic acid* which crystallised from acetic acid in needles (65 mg.), m. p. 224—226° (decomp.) (Found: C, 39·2; H, 3·5; Br, 29·0. $C_9H_9O_5Br$ requires C, 39·0; H, 3·5; Br, 28·8%). Starting material (55 mg.) was recovered from the acetone mother-liquors.

I am indebted to Dr. L. A. Duncanson for determining the infra-red absorption spectra; to Mr. H. G. Hemming for the biological assay; to Mr. P. J. Suter for assistance in the preparation of 2-bromo-3 : 5-dimethoxyphenol; and to many colleagues for their suggestions and criticisms.

Imperial Chemical Industries Limited,
Butterwick Research Laboratories,
The Frythe, Welwyn, Herts.

[*Received, April 6th*, 1954.]

Mycobactin. A Growth Factor for Mycobacterium johnei. *Part II.* Degradation, and Identification of Fragments.*

By G. A. Snow.

[Reprint Order No. 5112.]

Mycobactin has been subjected to a number of degradative procedures, and evidence is given of the presence of the following fragments: *trans*-octadec-2-enoic acid, 2-hydroxy-6-methylbenzoic acid, L-serine, and L-2-amino-6-hydroxyaminohexanoic acid. The last compound is a new and unusual type of amino-acid. The presence of an aliphatic acid of equivalent weight about 130 was also indicated.

Mycobactin is a growth factor for *Mycobacterium johnei*, isolated from *Myco. phlei*. Its extraction and general properties were described in Part I * in which evidence was presented that its empirical formula is $C_{47}H_{75}O_{10}N_5$. Among the degradation experiments now described, acid hydrolysis provided the principal information about the general structure. Action of aqueous acid yielded mainly *trans*-octadec-2-enoic acid, *m*-cresol, L-serine, a strongly reducing amino-acid, carbon dioxide, and, apparently an aliphatic acid, which was not obtained pure. Lysine was liberated in small amounts. Other degradations gave products which were apparently related to the fragments isolated from acid hydrolysis.

The ether-soluble products of acid hydrolysis were largely separated by distillation and identified by the usual methods. The water-soluble fraction was chromatographed on cation-exchange resin, and yielded crystalline L-serine and a compound which had the properties of an amino-acid, but also had strong reducing properties. This second substance seemed homogeneous and gave a single spot on paper chromatography, the position of the spot varying according to whether the solution applied to the paper was neutral or acid. The spots were shown in the same positions by either a ninhydrin spray or a spray designed to reveal reducing compounds. Analysis of crystalline salts supported the formula $C_6H_{14}O_3N_2$ for the amino-acid. The reducing action suggested that the compound must contain either a hydroxyamino- or a hydrazine group or possibly a $\cdot C(OH){:}C(OH)\cdot$ or $\cdot C(OH){:}C(NH_2)\cdot$ group. Among a number of hydrazines tested none was found to reduce alkaline triphenyltetrazolium chloride, whilst in a group of hydroxylamines all resembled the degradation product in giving an immediate red colour with this reagent. Compounds containing the groups $\cdot C(OH){:}C(OH)\cdot$ or $\cdot C(OH){:}C(NH_2)\cdot$ usually reduce iodine in acid, whereas the product from mycobactin only reduced it in neutral or alkaline solution. The compound could be reduced to lysine either by reaction with hydriodic acid or by catalytic hydrogenation, during which two atoms of hydrogen were taken up per molecule. This suggested strongly that the substance was either 2-amino-6-hydroxyamino- (I) or 6-amino-2-hydroxyamino-hexanoic acid (II). Further evidence of the presence of a hydroxyamino-group was obtained by oxidation with

$HO\cdot NH\cdot[CH_2]_4\cdot CH(NH_2)\cdot CO_2H$ (I) $NH_2\cdot[CH_2]_4\cdot CH(NH\cdot OH)\cdot CO_2H$ (II)

periodic acid, requiring 1 mol. of periodic acid per mol. of hydroxyamino-acid. This might be expected to yield an oxime, and in fact, the crude oxidation product on hydrolysis gave a solution which showed a positive reaction for hydroxylamine. Paper chromatography showed the oxidation product to be complex; it is possible that geometrical isomers were formed. Acetylation of the reducing amino-acid gave a non-crystalline non-reducing derivative shown by titration to be mainly the diacetate. It behaved as a typical hydroxamic acid, giving a strong reddish-purple ferric chloride reaction; titration showed it to be dibasic, the stronger acid group (pK 3·7) being presumably the carboxyl and the weaker (pK 9) the hydroxamic acid. Titration of the untreated reducing material also supported its formulation as an amino-hydroxyamino-

* Part I, Francis, Macturk, Madinaveitia, and Snow, *Biochem. J.*, 1953, **55**, 596.

acid. Alkali titrations showed an ionising group having a pK value of approx. 9·6 (the amino-group), and acid titration gave indications of two ionising groups, one with a pK of about 5·2 (probably the hydroxyamino-group) and the other of much lower pK (the carboxyl group). In glacial acetic acid the titration curve showed a single inflection after the addition of 2 equivs. of perchloric acid, corresponding to neutralisation of both basic groups.

In order to decide between structures (I) and (II) reference was made to a number of α-hydroxyamino-acids. These compounds had reducing properties similar to those of the product from mycobactin, though the " reducing values " given on oxidation with alkaline ferricyanide were somewhat lower and more variable. The α-hydroxyamino-acids reacted in a characteristic way with periodic acid, giving 1 mol. of carbon dioxide and forming aldehydes; 2—2·5 mols. of periodic acid were taken up and the hydroxyamino-group appeared to be converted into oxides of nitrogen. This behaviour differed from that of the product from mycobactin, which was oxidised with the uptake of 1 mol. of periodic acid without the production of carbon dioxide or aldehyde. The degradation product has therefore been assigned formula (I). When mycobactin was degraded with hydriodic acid, alanine and lysine were isolated, resulting from the reduction of serine and 2-amino-6-hydroxyaminohexanoic acid, respectively. The L-configuration of the lysine established the L-configuration of the hydroxyamino-acid. It could be shown that the " reducing value " of acid hydrolysates of mycobactin reached a maximum value of 13·0 equivs. per mole after 1·5—3 hours' hydrolysis. The corresponding reducing value of the pure hydroxyamino-acid was 7·25 equivs. per mole, so that each molecule of mycobactin must yield 2 mols. of the hydroxyamino-acid. This was confirmed by the finding that, during the degradation with hydriodic acid, up to 1·5 mols. of lysine were isolated as crystalline hydrochloride. In all acid hydrolyses some lysine could be demonstrated by paper chromatography; the amount was small. It may represent a degradation product of the hydroxyamino-acid. Experiments with varying periods of acid hydrolysis showed that the reducing value rose to a maximum and then slowly declined as the acid treatment was prolonged, and this is evidence that some secondary breakdown of the hydroxyamino-acid does occur. However, it is also possible that the lysine may be derived from a close relative of mycobactin which has not been separated by the purification methods.

Since it has been shown that acid hydrolysis produces 1 mol. of serine and 2 mol. of 2-amino-6-hydroxyaminohexanoic acid, these amino-acid fragments account for all the five nitrogen atoms known to be present in mycobactin.

Acid hydrolysis yields a small fraction insoluble in ether but soluble in butanol. Part of this fraction represents incompletely hydrolysed intermediates, but even after prolonged hydrolysis some unidentified butanol-soluble material remains, which appears to arise from side reactions.

Various other degradation methods have given three related phenolic compounds, *viz.*, *m*-cresol and 2-hydroxy-6-methylbenzoic acid and the corresponding amide. The yields of these compounds suggested that they all represented a single residue in the whole molecule. Experiment showed that 2-hydroxy-6-methylbenzoic acid was readily decarboxylated by boiling 5N-hydrochloric acid, but that in the presence of 20% v/v methanol decarboxylation was lessened and part of the original acid could be recovered. This behaviour paralleled the observation that when mycobactin was hydrolysed with aqueous acid only *m*-cresol was isolated, whilst in the presence of 20% v/v methanol both 2-hydroxy-6-methylbenzoic acid and *m*-cresol were obtained. In the aqueous hydrolysis nearly 1 mole of carbon dioxide was liberated per mole of mycobactin. Both the hydroxy-acid and *m*-cresol were also obtained in alkali fusion. There is thus reason to believe that 2-hydroxy-6-methylbenzoic acid is the fragment existing in the original molecule, decarboxylation occurring during acid hydrolysis. When mycobactin is submitted to drastic alkaline hydrolysis or to pyrolysis, the phenolic fragment isolated is 2-hydroxy-6-methylbenzamide. This amide is exceptionally resistant to acid hydrolysis, much remaining unchanged after prolonged boiling with 50% sulphuric acid. It was not possible to degrade the amide by acid treatment, without simultaneous decarboxylation. It thus seems unlikely that the phenolic acid could be present as a simple amide in mycobactin.

Moreover, it has already been shown that all the nitrogen in the molecule can be accounted for by the serine and 2-amino-6-hydroxyaminohexanoic acid residues. The production of the amide must therefore arise from some structure involving one of these compounds which can give the phenolic acid under conditions of acid hydrolysis. It is likely that one of the nitrogen atoms of the amino-acid fragments is attached to the carboxyl group of the phenolic acid in mycobactin.

The fatty acid fragment obtained by hydrolysis with aqueous acid was *trans*-octadec-2-enoic acid, but in the presence of 20% v/v methanol considerable esterification occurred during the hydrolysis. In alkali fusion, as would be expected, the fatty product isolated was palmitic acid.

Experimental

All melting points are corrected.

Electrometric Titrations.—Titrations were carried out on a semimicro-scale with a glass electrode and saturated calomel reference electrode connected to the titration chamber by a capillary bridge, reagents being delivered from a micrometer syringe. Titrations in glacial acetic acid were performed similarly except that precautions were taken to exclude moisture, and the bridge used in this case was filled with lithium chloride solution in glacial acetic acid; with this assembly the glass electrode was positive to the calomel electrode.

Reducing Values.—A reducing substance was isolated in the course of the degradations. It was conveniently estimated by oxidation with alkaline ferricyanide by Hanes's method (*Biochem. J.*, 1929, **23**, 99) for reducing sugars. The results were expressed as "reducing value" in equivs. of thiosulphate per mole of reducing compound for compounds of known molecular weight, or equivs. of thiosulphate per mole of mycobactin for crude hydrolysates.

Oxidation with Periodic Acid.—For estimation of the loss of periodic acid in reaction with reducing compounds the following method was used. Periodic acid solution (0·5 c.c.; 0·2M) was added to a solution (1—2 c.c.) of the reducing compound, the quantity taken being such that the amount of periodic acid present was at least 1·5 times that required for oxidation, the periodic acid being assumed to be reduced to iodic acid. The mixture was stored for 2 hr. in an ice-bath and then treated with excess of potassium iodide and hydrochloric acid, and the liberated iodine titrated with 0·02N-sodium thiosulphate. For estimation of the evolution of carbon dioxide the reducing compound (about 20 μmole) was dissolved in water (1 c.c.) in one flask of the apparatus described by Van Slyke, MacFadyan, and Hamilton (*J. Biol. Chem.*, 1941, **141**, 671) for the titrimetric estimation of carbon dioxide. A small capsule containing periodic acid solution (0·4 c.c.; 0·2M) was placed in the same flask without mixing. The other flask received saturated barium hydroxide solution (1 c.c.). The apparatus was evacuated (water-pump), the tap closed, and the periodate mixed with the reducing solution. The reaction was allowed to proceed for 1 hr. at room temperature. The contents of the reaction flask were then warmed to 50°, and the water distilled into the barium hydroxide flask which was cooled in ice. Estimation of the precipitated barium carbonate was carried out as in the van Slyke method.

Paper Chromatography.—Chromatography was carried out by the descending technique, Whatman No. 54 papers being used. Two-dimensional runs were performed by Dent's method (*Biochem. J.*, 1948, **43**, 169), except that collidine–lutidine was used as the first solvent; phenol with ammonia was used as the second solvent. Other solvents used for one-dimensional chromatography were butanol–acetic acid containing the following proportions by volume: water 25, acetic acid 12, *n*-butanol to 100, and butanol–propanol–diethylamine having the proportions: water 25, propanol 28, diethylamine 2, *n*-butanol to 100. Amino-acids were detected by the conventional ninhydrin spray. Reducing substances were detected by spraying first with 0·1% triphenyltetrazolium chloride in butanol saturated with water; the papers were then dried and sprayed lightly with a solution containing aqueous sodium hydroxide (10 c.c.; 10N), ethanol (40 c.c.), and butanol (50 c.c.). The presence of a reducing compound was shown by the immediate production of a red spot; the sensitivity was comparable to that of ninhydrin.

Hydrolysis of Mycobactin with Aqueous Hydrochloric Acid.—Mycobactin (5 g.) was refluxed for 8 hr. with hydrochloric acid (500 c.c.; 5N), with a slow stream of nitrogen passing through the solution. The issuing gas was passed through bubblers containing saturated aqueous barium hydroxide (200 c.c.) to absorb the carbon dioxide evolved. After neutralisation of excess of barium hydroxide the precipitated barium carbonate was estimated acidimetrically; it was

equivalent to 244 mg. of carbon dioxide (*i.e.*, 0·96 mol.). During the hydrolysis, mycobactin did not pass completely into solution but was transformed into an oil which solidified to a wax on cooling. The solution after hydrolysis was extraced with ether (3 × 250 c.c.), the wax passing into the ether layer. The aqueous layer was evaporated under reduced pressure, and the residue dissolved in hydrochloric acid (20 c.c.; 5N) and re-extracted with ether (5 × 100 c.c.). This ether extract was combined with the first, dried ($MgSO_4$), and evaporated. The residue (2·70 g.) was a yellow, waxy, partly crystalline solid with a phenolic smell (fraction A). The aqueous layer was evaporated under reduced pressure, and the residue dissolved in water (50 c.c.) and extracted with butanol (3 × 50 c.c.). The aqueous layer and butanol extracts were evaporated under reduced pressure; the residue from butanol was a brown gum (0·32 g.; fraction B) and that from the aqueous layer an almost colourless gum (3·17 g.; fraction C).

Fraction A. The product was distilled under reduced pressure, three fractions being collected: A1, a mobile liquid (0·36 g.), b. p. 130—135° (bath temp.)/15 mm.; A2, a viscous oil (0·275 g.), b. p. 120—130° (bath temp.)/0·2 mm.; and A3, a waxy solid (1·36 g.), b. p. 200—210° (bath temp.)/0·2 mm. Fractions A1 and A2 showed some overlap in properties; A1 was predominantly phenolic and A2 contained acidic material. Both fractions were treated with sodium carbonate solution (2 c.c.; 0·5M) and steam-distilled. The distillates (30 c.c.) were extracted with ether (3 × 30 c.c.), the extracts dried ($MgSO_4$), and the solvent removed. The products (306 mg. from A1, 145 mg. from A2) were combined, and the resulting oil was identified as *m*-cresol. It gave with ferric chloride a green colour in ethanol and a violet-blue colour in water; the carboxymethyl ether had m. p. and mixed m. p. 101—103° (Found: C, 65·35; H, 5·95. Calc. for $C_9H_{10}O_3$: C, 65·05; H, 6·05%); the 3:5-dinitrobenzoate had m. p. and mixed m. p. 165·5° (Found: C, 55·8; H, 3·4; N, 9·5. Calc. for $C_{14}H_{10}O_6N_2$: C, 55·6; H, 3·3; N, 9·3%); the α-naphthylurethane had m. p. and mixed m. p. 129—130° (Found: C, 77·95; H, 5·5; N, 5·35. Calc. for $C_{18}H_{15}O_2N$: C, 78·0; H, 5·45; N, 5·05%).

The residual solutions from fractions A1 and A2 were acidified, saturated with sodium chloride, and extracted three times with an equal volume of ether. The extract was dried ($MgSO_4$), and the solvent removed. The combined residues (129 mg. from A1, 146 mg. from A2) formed a viscous oil which appeared to contain an aliphatic acid (equiv., *ca.* 130). This hydrolysis did not, however, give a fragment sufficiently pure for identification; the acid was better obtained from a partial degradation product of mycobactin and will be discussed in a later paper.

A solution of fraction A3 in light petroleum was clarified by filtration, and solvent evaporated. The residue, crystallised successively from acetone and methanol, formed rhombic leaflets or needles, m. p. 58·5°, of *trans*-octadec-2-enoic acid. It reduced permanganate in acetone, but did not reduce bromine in carbon tetrachloride (Found: C, 76·6; H, 12·1%; equiv., by titration, 282. Calc. for $C_{18}H_{34}O_2$: C, 76·55; H, 12·1%; equiv., 282). It did not depress the m. p. of the synthetic acid (Ponzio, *Gazzetta*, 1904, **34**, II, 77; 1905, **35**, II, 569). Derivatives were also prepared from the acid obtained by degradation and from the synthetic acid: p-*bromophenacyl* ester, m. p. and mixed m. p. 88·5—89·5° from light petroleum (Found: C, 64·9; H, 7·8; Br, 15·9. $C_{26}H_{39}O_3Br$ requires C, 65·1; H, 8·2; Br, 16·7%); *benzylthiuronium* salt, m. p. and mixed m. p. 152—153°, from acetone (Found: C, 69·5; H, 9·8; S, 7·3. $C_{18}H_{34}O_2,C_8H_{10}N_2S$ requires C, 69·6; H, 9·9; S, 7·2%). The infra-red spectra of the acids, natural and synthetic, were identical and exhibited bands characteristic of an αβ-unsaturated acid.

Fraction C. The crude fraction (3·17 g.) contained ionisable chlorine equivalent to 0·95 g. of hydrogen chloride, had reducing properties, and gave a ninhydrin reaction. An aqueous solution was submitted to two-dimensional paper chromatography; reaction with ninhydrin revealed three principal spots, of which two corresponded with serine and lysine. The third did not correspond with a known amino-acid and its position would be represented on Dent's map (*loc. cit.*) as R_F 0·73 (phenol–ammonia), 0·23 (collidine).

No reducing substance was detectable after paper chromatography with neutral or basic solvents. A spot representing the reducing material could, however, be detected when butanol–acetic acid was used for development. The R_F values of the reducing material and of compounds reacting with ninhydrin were:

ninhydrin spray, 0·09 (lysine), 0·14 (serine), 0·21; triphenyltetrazolium spray, 0·21

The third spot obtained by conventional two-dimensional paper chromatography was evidently an artefact produced by oxidation of the reducing substance.

Separation of the components of fraction C was achieved by use of Partridge and Westall's method (*Biochem. J.*, 1949, **44**, 418, 521). Fraction C (3·10 g.), dissolved in water (65 c.c.),

was applied slowly to a column (85 × 0·67 cm.) of Zeo-Karb 215 (15·5 g.; 80—120 mesh); all the water-soluble material was held by the resin. A small conductivity cell, registering with a drum recorder, was attached to the end of the column, and the basic compounds were then displaced by slow passage of aqueous ammonia (0·15N), 4-c.c. fractions of the effluent being collected. The pH and reducing value of each fraction were measured and one-dimensional paper chromatograms were run, with butanol–acetic acid as solvent. The paper chromatograms indicated the presence of the two main well-separated components. The first component (fraction C1, tubes 49—54) corresponded chromatographically with serine. The emergence of the second component (fraction C2, tubes 57—63) was accompanied by a sharp rise in conductivity and pH, and the appearance of reducing properties. These properties then remained almost constant until a further rise in conductivity indicated the appearance of the ammonia front. Beyond this point the emergent solution gave no reducing reaction, but showed the presence of a little ninhydrin-reacting substance corresponding chromatographically to lysine; this portion was not further examined.

The aqueous solution containing fraction C1 was evaporated, giving a partly crystalline residue (0·40 g.). This was crystallised from aqueous solution by addition of ethanol, and identified as L-serine, $[\alpha]_D^{23}$ −6·4° (*c*, 6·5 in H_2O), m. p. 226—227° (decomp.) (Found: C, 34·4; H, 6·75; N, 13·15. Calc. for $C_3H_7O_3N$: C, 34·3; H, 6·7; N, 13·3%). It gave a single spot on two-dimensional paper chromatography alone or admixed with authentic serine; after treatment with hydriodic acid (9 hr.' refluxing with constant-boiling acid) the serine spot was replaced by a spot characteristic of alanine. With *p*-hydroxyazobenzene-*p'*-sulphonic acid it formed a salt which could be crystallised from water (Found: C, 44·85; H, 4·85; N, 10·5, 10·6. Calc. for $C_3H_7O_3N,C_{12}H_{10}O_4N_2S,H_2O$: C, 44·9; H, 4·8; N, 10·5%). In some separations the serine was incompletely held by the resin, and part passed into the effluent as the hydrochloride during application of the crude hydrolysate to the column. This did not however interfere with the separation.

The aqueous solution containing fraction C2 was evaporated under reduced pressure, leaving an almost colourless solid, m. p. 223—225° (decomp.). The substance could be precipitated from aqueous solution by addition of ethanol or methanol, but no crystallisation could be achieved. It appeared to be homogeneous, however. Paper chromatography with butanol–acetic acid as solvent yielded a single spot (R_F 0·30) detectable with ninhydrin. The hydrochloride of this substance, obtained by use of excess of hydrochloric acid and evaporation, gave a single spot with a lower R_F value (0·21), corresponding to the third spot in the paper chromatograms on the unseparated fraction C. When chromatograms of C2 and its hydrochloride were sprayed with triphenyltetrazolium spray, single spots were revealed at positions identical with those of the ninhydrin spots. The properties of C2 described below led to its formulation as L-2-*amino*-6-*hydroxyaminohexanoic acid*. It had $[\alpha]_D^{20}$ +6·3° ± 0·5° (*c*, 5·0 in H_2O), $[\alpha]_D^{18}$ +23·9° ± 0·5° (*c*, 5·1 in N-HCl) (Found: C, 44·1; H, 8·1; N, 16·9. $C_6H_{14}O_3N_2$ requires C, 44·4; H, 8·7; N, 17·3%). The crystalline *5-nitrobarbiturate* was prepared by dissolving fraction C2 (0·13 g.) in warm water (5 c.c.) with 5-nitrobarbituric acid trihydrate (0·17 g.), allowing the solution to cool slowly, and recrystallising the product (0·21 g.) twice from water; the rhombic prisms charred above 200° without a definite m. p. (Found: C, 34·35; H, 5·5; N, 19·74; loss of wt. when dried at 120°, 5·5. $C_6H_{14}O_3N_2,C_4H_3O_5N_3,H_2O$ requires C, 34·0; H, 5·4; N, 19·8; H_2O, 5·1%). A second salt was obtained when a solution of fraction C2 (0·05 g.) and 2-nitroindane-1 : 3-dione (0·05 g.) in water (3 c.c.) cooled slowly. The product (0·06 g.) was recrystallised twice from water yielding the *salt* of 2-nitroindane-1 : 3-dione as pale yellow crystals, m. p. 217—217·5° (decomp.) (Found: C, 51·0; H, 5·2; N, 11·9. $C_6H_{14}O_3N_2,C_9H_5O_4N$ requires C, 51·0; H, 5·4; N, 11·9%). Fraction C2 was very soluble in water but insoluble in neutral organic solvents; the aqueous solution had pH *ca.* 6·8. Neutral solutions absorbed oxygen from the air, but acid solutions were more stable. The solid material was best kept *in vacuo* over a desiccant. It showed the typical properties of an α-amino-acid: reaction with ninhydrin gave a blue colour; the carbon dioxide evolved was estimated by van Slyke's method (*loc. cit.*), giving a value of 0·93 mol. of carbon dioxide (mol. wt. 162 being assumed). A cold aqueous solution shaken with cupric carbonate gave a deep blue solution, together with some slight reduction to cuprous oxide. It gave no precipitate with the common precipitants for organic bases except phosphotungstic acid which yielded a sticky intractable product. It had strong reducing properties, reducing Fehling's solution or silver nitrate solution on gentle warming, iodine in neutral or alkaline, but not acid solution, and alkaline triphenyltetrazolium chloride. The aqueous solution shaken with lead peroxide gave no colour; 2 : 4-dinitrophenylhydrazine in acid solution did not yield a precipitate or change

colour; tests for sugars were negative. Reducing values of fraction C2 and its salts in equivs. per mole were: fraction C2, 7·25; 5-nitrobarbiturate, 7·22; 2-nitroindane-1 : 3-dione salt, 7·45. The absorption spectrum of fraction C2 showed a maximum at 219 mμ (ε, 2700 in water) with no absorption bands at longer wave-lengths. Electrometric titrations of 0·2M- and 0·1M-solutions with, respectively, N-hydrochloric acid and 0·03N-barium hydroxide, and of a 0·02M-solution in glacial acetic acid with 0·5N-perchloric acid were carried out. Fraction C2 (45 mg.), hydrogenated with Adams's catalyst (25 mg.) in water (3 c.c.), took up 1·05 mol. of hydrogen. The alkaline product was identified as lysine by paper chromatography and as picrate and dihydrochloride, m. p. 194—196° (Found: C, 32·95; H, 7·5; N, 12·75. Calc. for $C_6H_{12}O_2N_2,2HCl$: C, 32·9; H, 7·4; N, 12·8%). Fraction C2 could also be converted into lysine by refluxing constant-boiling hydriodic acid.

Fraction C2 (85 mg.) was acetylated in water (2 c.c.) at 0° by gradual simultaneous addition of acetic anhydride (0·4 c.c.) and 10N-sodium hydroxide in equivalent amount. The addition was made with constant stirring during 30 min.; a slow stream of nitrogen was bubbled through the solution during the acetylation, and any excess of alkali was avoided. Stirring was continued for a further 30 min., then sufficient alkali was added to make the solution 0·2N, and the solution kept at 0° for 30 min. It was acidified with 10N-sulphuric acid and extracted with 17% v/v butanol in chloroform (6 × 2 vols.). The extract was filtered through a dry filter-paper and evaporated under reduced pressure, leaving a colourless gum (114 mg.) which could not be crystallised. The equivalent weights represented by the two steps in the electrometric titration curve suggested that the product consisted of about 80% diacetate (dibasic acid) and 20% triacetate (monobasic acid).

A solution of fraction C2 (146 mg.) in water (5 c.c.) was cooled in ice, periodic acid (0·2M; 6 c.c.) was added, and the solution was kept for 2 hr. in an ice-bath. It was then diluted to 25 c.c.; titration of an aliquot portion (0·5 c.c.) indicated the reduction of 2·08 equivs. per mole of C2. Barium hydroxide (0·3M; 6·1 c.c.) was added to the solution to bring the pH to 7·0, and the solution boiled, cooled, and set aside. The precipitated salts were filtered off, the filtrate evaporated, and the residue dissolved in the minimum of water; this solution was filtered and again evaporated. The residue (170 mg.) still contained a little inorganic material. Paper chromatography with phenol–ammonia gave one spot, R_F 0·71, and with butanol–propanol–diethylamine two main spots, R_F 0·05 and 0·16. The product was not further separated. The crude oxidation product gave a strongly positive test for the oxime group (Feigl, "Spot Tests," 1939, 2nd. edn., p. 290).

In order to establish the position of the hydroxyamino-group in fraction C2 its reactions were compared with those of the following α-hydroxyamino-acids, kindly supplied by Dr. G. Swain: (*a*) hydroxyaminoacetic acid, (*b*) 2-hydroxyaminohexanoic acid, (*c*) α-hydroxyamino-β-phenylpropionic acid. All three resembled C2 in immediately reducing alkaline triphenyltetrazolium chloride. They also reacted with ninhydrin to produce 1 mol. of carbon dioxide with the formation of aldehydes. Other properties were as follows:

		α-Hydroxyamino-acids		
Compound:	C2	(*a*)	(*b*)	(*c*)
Ninhydrin colour	Intense blue	Weak yellow or orange		
Aqueous solution with $CuCO_3$	Blue	Blue (all showed reduction on being warmed)	Blue	Colourless
Reducing values	7·25	4·1 *	5·2 *	5·8 *
Periodate oxidation:				
(*a*) Mol. consumed	1·0	2·45	2·2	2·4
(*b*) Mol. CO_2 liberated	0·0		1·0	

* These figures varied somewhat according to concentration.

A compound believed to be DL-6-amino-2-hydroxyaminohexanoic acid was strongly reducing but gave a pale colour with ninhydrin, and no blue colour with copper carbonate; the crystals of the 5-nitrobarbiturate were of a different form from those of the corresponding derivative of fraction C2.

Fraction B. This fraction appeared to be a complex mixture and was thought likely to contain some incompletely hydrolysed material. The fraction (0·32 g.) was further hydrolysed by refluxing it for 16 hr. with hydrochloric acid (5N; 50 c.c.). The product was separated into three fractions corresponding to the three main fractions isolated in the original hydrolysis: ether-soluble (0·04 g.), butanol-soluble (0·13 g.), and water-soluble (0·16 g.). The water-soluble

fraction had reducing properties, and paper chromatography indicated the presence of serine, lysine, and 2-amino-6-hydroxyaminohexanoic acid. The ether-soluble fraction gave a violet colour with ferric chloride.

Progressive Acid Hydrolysis of Mycobactin.—Portions of mycobactin (80 mg.) were refluxed with hydrochloric acid (5N; 8 c.c.) for varying periods. The resultant solutions were cooled, diluted, and extracted with ether, and the aqueous solutions evaporated under reduced pressure. The residues were dissolved in water and estimations of the reducing compounds present carried out upon aliquot portions:

Time of hydrolysis (hr.)	½	¾	1·5	3	6	12	24	96
Reducing value (equiv. per mole of mycobactin)	9·3	11·0	13·0	12·5	12·1	11·7	11·3	8·5

Synthesis of Hydroxyamino-acids (By G. SWAIN).—Traube's method (*Ber.*, 1895, **28**, 2300) gave *2-hydroxyaminohexanoic acid*, m. p. 168—170° (decomp.), from 50% aqueous ethanol (Found: C, 48·9; H, 8·8; N, 9·95. $C_6H_{13}O_3N$ requires C, 49·0; H, 8·9; N, 9·5%). Diethyl 4-phthalimidobutylmalonate, by the same procedure, yielded a crystalline product, m. p. 168—170° (sinters 160°), which was probably mainly 6-amino-2-hydroxyaminohexanoic acid, though the analysis was unsatisfactory. It gave a *5-nitrobarbiturate* as colourless rhombs without definite m. p. (charred at 220—240°) (Found: C, 31·4; H, 4·85; N, 19·3. $C_6H_{14}O_3N_2,2C_4H_3O_5N_3,2H_2O$ requires C, 30·9; H, 4·4; N, 20·6%).

Reactions of Hydrazines and Hydroxylamines with Triphenyltetrazolium Chloride.—Triphenyltetrazolium chloride (about 1 mg.) was dissolved in a drop of an aqueous solution of the test compound, on a tile, and a drop of 2N-sodium hydroxide added. Immediate development of a deep red colour was taken as a positive reaction. Positive reactions were given by the following hydroxylamines: hydroxylamine, *N*-ethylhydroxylamine, α-hydroxyamino*iso*butyl cyanide, *N*-hydroxymorpholine, and a series of α-hydroxyamino-fatty acids. The following hydrazines gave negative reactions: methylhydrazine, phenylhydrazine, 1 : 1′-dicarboxy-*NN*′-di*iso*propylhydrazine.

Acid Hydrolysis of Mycobactin in the Presence of Methanol.—Mycobactin (2 g.) was dissolved in methanol (40 c.c.), the solution poured with stirring into hydrochloric acid (5N; 160 c.c.), and the resulting suspension refluxed for 12 hr., then cooled, diluted with water (200 c.c.), and extracted with ether (3 × 200 c.c.). The aqueous layer appeared to be similar to that obtained by hydrolysis in the absence of methanol; it was separated as described above for fraction C. The ether layer was extracted first with aqueous sodium carbonate (3 × 300 c.c.) and then with aqueous sodium hydroxide (3 × 300 c.c.). The ether solution was washed with water and dried ($MgSO_4$), and the solvent removed, leaving an oily residue (0·39 g.; fraction D). The sodium hydroxide extract was acidified with hydrochloric acid and steam-distilled. The distillate was extracted with ether, the extract dried, and the solvent removed, leaving an oily residue (0·11 g.) which was distilled and identified as *m*-cresol. The solution after steam-distillation was also extracted with ether; the extract, when dried and evaporated, left a residue containing a little acidic material (0·08 g.) which was combined with fraction E (see below). The sodium carbonate extract was acidified with hydrochloric acid and extracted with ether. The ether solution was dried and evaporated, leaving a brown, waxy, partly crystalline residue (0·32 g.; fraction E).

Fraction D. The product was distilled at 140—160°/0·04 mm. (oil-bath temp.), yielding an oil, m. p. 13—13·5°, apparently slightly impure methyl octadec-2-enoate. It was neutral, free from nitrogen, and reduced permanganate in acetone but not bromine in carbon tetrachloride; there was no reaction for carbonyl groups. Saponification with 2N-sodium hydroxide gave methanol, detected by Boos's method (*Analyt. Chem.*, 1948, **20**, 964), and an acid, m. p. 58·5° after crystallisation, identified as *trans*-octadec-2-enoic acid.

Fraction E. The waxy product (0·40 g.), yielded a crystalline sublimate (0·12 g.) at 100—130°/0·04 mm. (oil-bath temp.) and a waxy solid (0·15 g.) at 160—180°/0·04 mm.; the latter gave octadec-2-enoic acid on recrystallisation. The sublimate, crystallised from water and chloroform, had m. p. 170—170·5°, and was shown to be 2-hydroxy-6-methylbenzoic acid (Found: C, 63·4; H, 5·7%; equiv., by titration, 152. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·3%; equiv., 152). There was no depression of m. p. with a specimen (m. p. 169·5—170·5°) kindly supplied by Professor H. Raistrick; ultra-violet spectra measured in acid and alkaline solutions and at pH 8·0 were identical in every detail for the two specimens.

Degradation of Mycobactin with Hydriodic Acid.—Mycobactin (2 g.) was refluxed for 9 hr. with constant-boiling hydriodic acid (40 c.c.), and the solution poured into water (120 c.c.). It was extracted with ether (4 × 80 c.c.), and the aqueous layer evaporated under reduced

pressure. The ether-soluble fraction contained fatty acid and phenolic products containing iodine; it was not further examined. The residue from the aqueous layer was dissolved in water (40 c.c.), and iodide removed by shaking with an excess of freshly-precipitated silver chloride. The silver halides were filtered off, and the filtrate evaporated under reduced pressure, leaving a clear gum (1·13 g.) which tended to crystallise. Slow crystallisation from methanol (25 c.c.) by progressive addition of ether gave first a product (5 mg.), m. p. 252—253°, which was probably lysine monohydrochloride (Found: C, 36·2; H, 8·7. Calc. for $C_6H_{14}O_2N_2,HCl,H_2O$: C, 35·9; H, 8·5%), then crystalline L-lysine dihydrochloride (0·69 g.), m. p. 194—196° (decomp.) after recrystallisation, $[\alpha]_D^{21}$ +16·5° in N-hydrochloric acid (*c*, 3·0) (Found: C, 33·1; H, 7·3; N, 12·95. Calc. for $C_6H_{14}O_2N_2,2HCl$: C, 32·9; H, 7·35; N, 12·8%). The picrate had m. p. 266° (explodes) (Found: C, 38·3; H, 4·6; N, 18·65. Calc. for $C_6H_{14}O_2N_2,C_6H_3O_7N_3$: C, 38·4; H, 4·55; N, 18·65%).

Paper chromatography of the residue after crystallisation of the lysine indicated the presence of much alanine together with a small amount of residual lysine.

Alkali Fusion.—Mycobactin (1·5 g.) was added slowly (30 min.) to a melt containing sodium hydroxide (7·5 g.) and potassium hydroxide (4·5 g.) at 250°. The temperature of the melt was then raised to 290° for a further 1½ hr. An alkaline gas identified as ammonia was evolved and was trapped in bubblers containing N-hydrochloric acid. The melt was cooled and dissolved in water (30 c.c.), and the solution treated with sodium chloride solution (5M; 60 c.c.). The precipitate was filtered off (fraction F) and washed with brine. Carbon dioxide was passed through the filtrate until the pH was 8—9 and the latter was steam-distilled. The distillate was extracted with ether, the extract dried, and the solvent removed, leaving *m*-cresol (0·06 g.). The solution remaining after steam-distillation was acidified with hydrochloric acid and steam-distilled, until no more acid was evolved. The distillate was neutralised with sodium hydroxide and evaporated under reduced pressure, leaving a salt (0·83 g.; fraction G).

Fraction F. The sodium salt was dissolved in hot water (30 c.c.), and the solution acidified, cooled, and extracted with ether. The extract was dried and the solvent removed, leaving a waxy crystalline residue (0·36 g.). This was repeatedly crystallised from acetone and gave a product which appeared to be substantially palmitic acid although the m. p. could not be raised above 59°. It had equiv. 255 by titration (Calc.: 256), and gave a benzylthiuronium salt, m. p. 141° (Found: C, 68·2; H, 9·85; S, 7·6. Calc. for $C_{16}H_{32}O_2,C_8H_{10}N_2S$: C, 68·2; H, 10·0; S, 7·6%). The acid was saturated, and its surface-spreading properties were identical with those of palmitic acid.

Fraction G. The sodium salt was dissolved in water (2 c.c.) and acidified with dilute sulphuric acid. A crystalline precipitate separated out. This was filtered off (0·05 g.), crystallised from chloroform, and identified as 2-hydroxy-6-methylbenzoic acid. The filtrate contained a mixture of volatile aliphatic acids, from which acetic acid was isolated as its *p*-bromophenacyl ester, m. p. and mixed m. p. 85—86° (Found: C, 46·85; H, 3·5; Br, 30·8. Calc. for $C_{10}H_9O_3Br$: C, 46·7; H, 3·5; Br, 31·1%). Another acid having a smell resembling that of valeric or hexanoic acid was not identified.

Hydrolysis of Mycobactin in Alkaline Solution.—Mycobactin (1 g.) was refluxed for 6 hr. with potassium hydroxide (10 g.) in 90% ethanol (30 c.c.) in a slow stream of nitrogen. The issuing gas was passed through traps containing hydrochloric acid. The volatile basic gas was estimated by titration and found to be equivalent to 0·11 g.-atom of nitrogen per mole of mycobactin. The alkaline hydrolysate was cooled and diluted with water (40 c.c.), and carbon dioxide was passed through until the pH was 8—9. A slimy precipitate separated and was centrifuged off, leaving a turbid solution. The remainder of the insoluble product separated as an interface on subsequent ether extraction. The combined insoluble product, washed and dried in a desiccator (0·23 g.), was a white, apparently polymeric, powder. The sodium carbonate solution extracted with ether (8 × 100 c.c.) contained a complex mixture of substances from which no pure compound has been separated. The ethereal extract was dried ($MgSO_4$), and the solvent removed. The residue (0·17 g.) was stirred with light petroleum and filtered; the filtrate was not further examined. The petroleum-insoluble product (0·05 g.) gave hexagonal plates (m. p. 199—200°), from water or xylene, identified as *2-hydroxy-6-methylbenzamide* after comparison with a synthetic specimen (see below). The two specimens showed no depression of m. p. when mixed, and their ultra-violet and infra-red spectra were identical. The solution in water was neutral and gave a deep violet colour with ferric chloride. Quantitative acetylation (method as in Part I, *loc. cit.*) gave 1·01 hydroxyl groups per molecule (Found: C, 63·4; H, 5·7; N, 9·45. $C_8H_9O_2N$ requires C, 63·5; H, 6·0; N, 9·3%).

Synthesis of 2-Hydroxy-6-methylbenzamide (with M. A. T. Rogers).—2 : 3 : 5-Trimethyl-

1 : 4-benzopyrone (Robertson, Waters, and Jones, *J.*, 1932, 1681) (3·0 g.) in chloroform (50 c.c.) was saturated with ozonised oxygen at 0° for 3 hr. 2N-Sodium hydroxide (25 c.c.) was added and the chloroform removed by a stream of air. The suspension was warmed for 30 min. at 50° and then to 100° with a further 10 c.c. of sodium hydroxide. Filtration and acidification yielded 2-hydroxy-6-methylbenzoic acid (1·58 g.), m. p. 166°. The recrystallised acid, m. p. 171—172° (0·92 g.), was treated in ether with a slight excess of diazomethane, giving the methyl ester, which was mixed with saturated methanolic ammonia (20 c.c.) and heated at 100° for 12 hr. in a sealed tube. Evaporation and crystallisation of the residue from water (charcoal) gave plates, m. p. 201° (Found: C, 63·45; H, 5·9; N, 9·15%).

Pyrolysis of Mycobactin.—Mycobactin (0·5 g.) was heated under reduced pressure in a small retort immersed in a metal-bath. Over a temperature range 190—250° at 0·07—0·12 mm. a crystalline product sublimed together with some waxy material and a dark oil. The crystals (23 mg.), washed with chloroform, were crystallised from water and identified as 2-hydroxy-6-methylbenzamide.

The author thanks Messrs. D. Mellor and J. C. B. Smith for valuable technical assistance.

Imperial Chemical Industries Limited,
Research Department, Manchester, 9. [*Received, March 12th,* 1954.]

The Pyrolysis of Chloroalkenes. Part I. Allyl Chloride.

By (Miss) A. M. Goodall and K. E. Howlett.

[Reprint Order No. 5076.]

Gaseous allyl chloride decomposes in the temperature range 370—475° by simultaneous non-chain, chain, and heterogeneous processes to yield, initially, allene and hydrogen chloride. The allene polymerises rapidly at these temperatures. By fractional distillation of the liquid reaction products some of the lower polymers have been identified. The pyrolysis of allyl chloride is the first dehydrochlorination which has been observed to be markedly heterogeneous under these experimental conditions.

In recent years the kinetics of the thermal decompositions of numerous chloroalkanes have been described (Barton, Head, and Williams, *J.*, 1952, 453; Howlett, *ibid.*, p. 3695; and references there cited). One general conclusion reached from these investigations is that a polychlorohydrocarbon decomposes, losing 1 mol. of hydrogen chloride and yielding a chloroalkene, much more rapidly than any subsequent reactions of these initial products. Thus, for the purpose of calculating rate constants, it has been assumed that the whole of the measured reaction refers to this first dehydrochlorination process. It is obviously desirable to check this by direct observation of the kinetics of decomposition of the pure chloroalkenes. No such physicochemical study has yet been reported. Allyl chloride was chosen as a representative unsaturated chloride. It was also hoped that suitable experimental conditions might be found for the production of allene or of methylacetylene, starting from allyl chloride.

Experimental

Apparatus and Materials.—The static apparatus employed for the kinetic work was essentially similar to that described by Barton and Howlett (*J.*, 1949, 155), and the results therefore refer to decomposition in vessels whose walls were covered with a coherent carbonaceous film.

In order to obtain the reaction products in quantity, dynamic experiments have also been performed. " Oxygen-free " nitrogen was purified over red-hot copper and passed through an oil flow-meter. It was then bubbled through an allyl chloride trap which could be kept at any desired temperature or by-passed if necessary. The gases passed through a 45-c.c. Pyrex tube reaction vessel of surface/volume ratio *ca.* 6 cm.$^{-1}$, in a manually operated, aluminium block, electric furnace. The reaction products were collected by passage through suitable traps and absorbents [*e.g.*, a 10° trap surmounted by a condenser; 2 water traps; 1 trap containing Ilosvay's reagent (cf. *Ber.*, 1899, **32**, 2698); magnesium–barium perchlorate; a trap kept at

−80°, and finally concentrated sulphuric acid, for the successive removal of a thin tar, hydrogen chloride, acetylenes, (water), unchanged allyl chloride, and finally olefins]. The temperature of the furnace was measured with a base-metal thermocouple calibrated immediately before use. The walls of the reaction vessels were covered with a carbonaceous film before the collection of products was attempted.

Allyl chloride was prepared from allyl alcohol (cf. Vogel, " Textbook of Practical Organic Chemistry," p. 276). The purified product was redistilled immediately before its admission to the reservoir trap attached to the apparatus; it had b. p. 45·2° (corr.), n_D^{23} 1·4137. It was rapidly degassed and, when not being volatilised into the reaction vessel, was kept in the dark at −80° in order to retard polymerisation (Staudinger and Fleitmann, *Annalen*, 1930, **480**, 92).

Results.—Maccoll (*J. Chem. Phys.*, 1949, **17**, 1350) reported that, under experimental conditions similar to ours, allyl bromide eliminates hydrogen bromide in the range 320—380°. Pressure increases in a constant-volume system were approximately 50% when the dehydrobromination approached completion. This is consistent with the formation of hydrogen bromide and a dimer of allene.

The kinetics of the decomposition of allyl chloride have been studied in the range 370—475°. The course of this reaction could not be followed by pressure changes, for these were complex. The products of reaction were therefore analysed for hydrogen chloride by condensation in a 5-c.c. liquid-air trap connected to the reaction vessel, and subsequent titration. When the vessel was opened to this trap after a " kinetic " run the pressure fell to 0·1—0·5 mm. It is thus clear that other cracking reactions producing hydrogen or methane cannot occur to any appreciable extent. After a number of overnight runs in which the decomposition was allowed to approach completion at about 450°, the final pressure was 1·6—1·7 times that initially admitted. The incompleteness of condensation after these long-term experiments suggests that slight cracking of the reaction products, subsequent to, and not simultaneous with the main process, had occurred after 15 hr. at 450°. In both long- and short-term runs, hydrogen chloride determinations invariably indicated greater extents of decomposition than did the pressure changes (in the latter calculation it was assumed that 1 mol. of reactant gave 2 mols. of product), and there was no constant ratio between these two apparent extents of reaction. The reported results are based upon the analyses and therefore refer to the dehydrochlorination of allyl chloride. Determinations of hydrogen chloride from the 15-hr. runs (necessarily rough and low on account of the 2—3 mm. residual pressure) indicated an average of *ca.* 90% decomposition in this sense.

The dehydrochlorination of allyl chloride follows a first-order law to at least 30% decomposition over the initial pressure range 10—100 mm., as shown in Table 1, where velocity constants at 458° are given for different initial concentrations of reactant. There is clearly no significant variation of velocity constant.

TABLE 1.

p_0 (mm.)	11	16	32	48	70
No. of runs	27	20	31	15	19
10^5k (sec.$^{-1}$) (mean)	23·6	25·0	26·2	24·4	26·2

The mean velocity constants obtained at different temperatures are shown in Table 2 and may be summarised by the method of least squares, giving equal statistical weight to each experiment, as $k = 10^{9\cdot10}e^{-42,500/RT}$ sec.$^{-1}$, for the rate constant of dehydrochlorination of allyl chloride in reaction vessels with product-fouled walls and of surface/volume ratio 2 cm.$^{-1}$. The reaction has also been studied in a packed vessel of surface/volume ratio 22 cm.$^{-1}$. These results are included (*p*) in Table 2. These velocity constants are 2—3 times those found in the unpacked vessel. The apparent activation energy of the overall reaction in the packed vessel (32 kcal./mole) is definitely lower than that in the " empty " vessel.

TABLE 2

Temp.	No. of runs	10^5k (sec.$^{-1}$) (mean)	Temp.	No. of runs	10^5k (sec.$^{-1}$) (mean)	Temp.	No. of runs	10^5k (sec.$^{-1}$) (mean)
475°	22	41·1	440° *p*	19	23·5	393°	7	1·26
469	23	36·1	421 *p*	8	14·2	380	6	1·07
458	112	25·2	420	12	4·80	378 *p*	7	2·54
457 *p*	17	40·3	397 *p*	7	5·91	370	7	0·418
440	17	10·6						

p = Packed reaction vessel.

Propylene is well established as a powerful inhibitor for the radical-chain decompositions of chlorohydrocarbons (Barton and Howlett, *J.*, 1951, 2033). Its effect upon the pyrolysis of allyl chloride has been studied in both packed and unpacked reaction vessels. A small decrease in velocity constant was observed on addition of propylene. Maximum inhibition was achieved with quite small amounts of this gas as is shown in Table 3, which gives some results obtained at

TABLE 3

p_0, C_3H_6 (mm.)	0	1·2	1·9	10·8	11·9	17·9
10^5k (sec.$^{-1}$)	25·2	20·0	17·5	19·1	22·3	18·2

458° with 33 mm. initial pressure of allyl chloride. For the later inhibited experiments, the propylene pressure was therefore kept between 5 and 10 mm. The first-order velocity constants found under these conditions were independent of the allyl chloride concentration and are given in Table 4.

TABLE 4

Temp.	420°	420° p	458°	458° p
No. of runs	6	14	30	29
10^5k (sec.$^{-1}$) mean	4·49	10·4	20·6	33·8

In a typical experiment for the collection and identification of the reaction products, nitrogen was passed through the flow apparatus at 4 c.c./min. (measured at 20°) for 175 hr., the furnace temperature being 505° ± 5°. During this time 104·2 g. of allyl chloride were volatilised and passed through the furnace with a hot contact time of 142 sec. The gas mixture entering the furnace contained about 40% of reactant, and hydrogen chloride titration showed that of the 1·36 moles passed through the furnace, 0·611 mole was decomposed. This corresponds to a velocity constant of 4×10^{-3} sec.$^{-1}$, *i.e.*, within a factor of 2 of that expected by extrapolation from the static results. This confirms that the same reaction as that measured kinetically is occurring in the dynamic runs. The total acetylenes were determined by Willstätter and Maschmann's modification of Ilosvay's test (*Ber.*, 1920, **53**, 939). About 2% of acetylenes were found, based upon the allyl chloride consumed. Allene, estimated by distilling the diluted sulphuric acid trap liquor into sodium hypoiodite and weighing the precipitated iodoform, averaged about 1% of the decomposed allyl chloride. Furthermore, the almost negligible increase in weight of the sulphuric acid trap indicated that the total olefins were of the same order as the allene. The main carbon balance was accounted for by the thin tar condensed at 10° immediately on leaving the furnace. The weight of this fraction was *ca.* 70% of the total possible allene formed. The remaining carbon was probably deposited as the carbonaceous layer in the furnace and exit tube, since deposition here was noticeably heavy. Fractional distillation of 10 g. of the tar gave a small amount boiling at *ca.* 50°, identified as allyl chloride, and then the following fractions which all showed unsaturation to bromine in carbon tetrachloride and were practically free from chlorine.

Boiling range	Wt., g.	Odour	n_D^{20}	M
61—68°	0·5	Sharp	1·4545	81
35—50/9 mm.	0·8	Turpentine	1·5122	—
50—70/9 mm.	0·4	Turpentine	—	—
71—80/9 mm.	0·4	Camphor	1·5478	—
80—105/9 mm.	0·7	Paraffin	1·5704	153
Residue	6·0	Burnt rubber	—	—

DISCUSSION

The tar fractionation products are almost identical in every respect with those obtained by Meinert and Hurd (*J. Amer. Chem. Soc.*, 1930, **52**, 4540) and Lebedev (*J. Russ. Phys. Chem. Soc.*, 1913, **45**, 1249) from the pyrolysis of allene. In particular, the fractions of M 81 and 153 correspond to Lebedev's reported dimer and tetramer of allene. Meinert and Hurd also found mainly liquid polymers with less than 10% of gaseous products under experimental conditions similar to ours. It seems, therefore, that, in the main, the pyrolysis of allyl chloride leads initially to allene and hydrogen chloride. The method is, however, quite unsuitable for producing allene or its isomers because allene polymerises at these temperatures faster than allyl chloride decomposes.

The decomposition of allyl chloride is the first gaseous dehydrochlorination which has

been observed to have an appreciable heterogeneous component even when reaction is conducted over a heavy carbonaceous surface. After correction of the observed velocity constants to zero surface/volume ratio, the homogeneous rate constant is found to be $k \simeq 10^{10\cdot1}e^{-46,000/RT}$ sec.$^{-1}$, whence the activation energy of the heterogeneous reaction is *ca.* 25 kcal./mole. This is definitely higher than that for the glass-catalysed heterogeneous pyrolysis of *tert.*-butyl chloride (Barton and Onyon, *Trans. Faraday Soc.*, 1949, **45**, 725). Over our temperature range the homogeneous reaction is predominant but, if rate measurements could be carried out at lower temperatures, the heterogeneous reaction would be important and a pronounced curve would be apparent in the Arrhenius plot.

The effect of propylene upon the reaction shows that it is mainly non-chain in character, but that in the unpacked reaction vessel about 10% of the total is of the radical-chain type. This radical reaction is shown to be homogeneous by comparing the results in packed and in unpacked reaction vessels in the presence of inhibitor. If all the observed heterogeneity were due to chain reaction, the maximally inhibited reaction rate constant would be independent of the surface/volume ratio. This is not found experimentally. Therefore, the heterogeneous reaction is at least partly non-chain in character. Also, the difference between the velocity constants for the inhibited and the uninhibited reaction, *i.e.*, the rate constant for the chain process, is the same in both reaction vessels, showing that the chain reaction is homogeneous and also that the heterogeneous reaction is entirely non-chain in character.

It seems likely that the low efficiency of both the homogeneous processes is the reason for the marked heterogeneity of the total reaction. Maccoll (*loc. cit.*) considered allyl bromide to decompose by splitting of a C–Br bond—a conclusion borne out by the activation energy. A different mechanism is obviously involved in the present case, for the activation energy which we find is similar to that found by Maccoll, in spite of the higher C–Hal bond energy in allyl chloride.

It is interesting to compare the rate of decomposition of allyl chloride with that for 1 : 2-dichloropropane (Barton and Head, *Trans. Faraday Soc.*, 1950, **46**, 114) because allyl chloride is probably amongst the monochloropropenes produced from the latter. In the temperature range investigated by Barton and Head the velocity constant for decomposition of allyl chloride averages about 13% of that for 1 : 2-dichloropropane. Thus if the velocity constants for the latter were computed for a 50% increase in pressure (which is probably a maximum), the error in assuming this to arise solely from the first reaction is less than 3%, which is not serious. In a series of 15-hr. runs, carried out above 700° K, Barton and Head's ratios of final to initial pressure (*ca.* 2·6) are just what would be expected from our results on the pyrolysis of allyl chloride.

BEDFORD COLLEGE, LONDON, N.W.1. [*Received, January 30th*, 1954.]

The Pyrolysis of Chloroalkenes. Part II. Trichloroethylene.*

By (MISS) A. M. GOODALL and K. E. HOWLETT.

[Reprint Order No. 5077.]

Trichloroethylene decomposes in the temperature range 385—445° and in vessels whose walls are covered with a carbonaceous layer by simultaneous homogeneous radical-chain and bimolecular mechanisms. The final reaction products are hydrogen chloride and hexachlorobenzene in theoretical yield. The chain reaction is inhibited relatively weakly by one of the reaction products and strongly by propylene and *n*-hexane. The pressure range investigated is 17—42 mm. and the reaction is discussed in connection with Slater's theory of unimolecular reactions.

SLATER (*Phil. Trans.*, 1953, *A*, **246**, 57) has concluded that only molecules with six or more atoms should show unimolecular rates of decomposition approaching k_∞ at pressures as

* Part I, preceding paper.

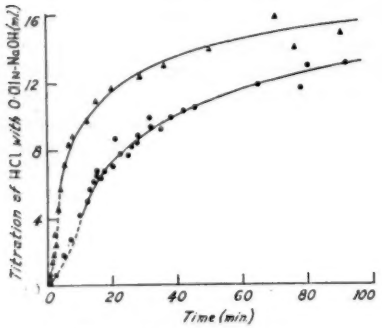
low as 2 atm. It was felt that trichloroethylene would provide a possible test of this conclusion because all the many dehydrohalogenations so far examined kinetically by the conventional static method (Biltz and Kuppers, *Ber.*, 1904, **37**, 2398; Lessig, *J. Phys. Chem.*, 1932, **36**, 2325; and the series of papers by Daniels, Vernon, Fugassi, and Veltman, *J. Amer. Chem. Soc.*, 1933, **55**, 922; 1938, **60**, 771; *J. Chem. Phys.*, 1939, **7**, 756; by Kistiakowsky, Brearley, and Stauffer, *J. Amer. Chem. Soc.*, 1936, **58**, 43; 1937, **59**, 165; by Maccoll, Green, Harden, and Thomas, *J. Chem. Phys.*, 1949, **17**, 1350; 1951, **19**, 977; 1953, **21**, 178; by Barton, Head, Howlett, Onyon, Williams, and Goodall, *J.*, 1949, 148, 155, 165; 1951, 2033, 2039; 1952, 453, 3695, 4487; 1953, 113, 945; and preceding paper; *Trans. Faraday Soc.*, 1949, **45**, 725, 735; 1950, **46**, 114; 1952, **48**, 25; *J. Amer. Chem. Soc.*, 1950, **72**, 988) have involved polyatomic molecules containing more than six atoms and none of them has shown a molecularity greater than unity. Trichloroethylene is a product of the pyrolysis of both tetrachloroethanes (Barton and Howlett, *J.*, 1951, 2033; Barton, *J.*, 1949, 148), and from some perfunctory experiments, its rate of reaction seemed to be negligible in comparison with the rates of decomposition of the saturated compounds. Another purpose of the present work was to re-examine this conclusion.

Experimental

Apparatus and Materials.—Both the static and the dynamic apparatus used were described in Part I (*loc. cit.*). Commercial trichloroethylene was shaken twice with concentrated sulphuric acid and once each with water, aqueous sodium hydrogen carbonate, and water. The liquid was dried, fractionated twice, and immediately admitted to the apparatus; it had b. p. 87·0° (corr.), n_D^{20} 1·4780, d_4^{20} 1·4616.

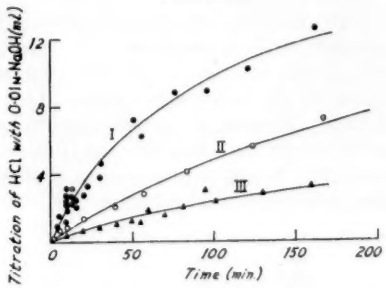
Results.—The pyrolysis of trichloroethylene was studied kinetically at 385—445°. The investigation was hampered by the deposition of a solid product in the stopcocks of the

Fig. 1.



● 410°, p_0 = 42·5 mm.
▲ 444·5°, p_0 = 42·5 mm.
Reactor volume = 190 ml.

Fig. 2.



I. 444·5°, 42·5 mm. C_2HCl_3 + 5 mm. C_3H_6.
II. 410°, 42·5 mm. C_2HCl_3 + 5 mm. C_3H_6.
III. 444·5°, 18·3 mm. C_2HCl_3 + 5 mm. C_3H_6.

apparatus even when these were heated to 100° (cf. Barton and Howlett, *loc. cit.*). Hence, after each few runs the static apparatus had perforce to be fillled with hydrogen, and the solid removed. As with allyl chloride (Part I), the pressure changes accompanying decomposition were complex, the pressure actually falling during the later stages of reaction, and the kinetics of the reaction were therefore followed by hydrogen chloride determinations. In a series of overnight experiments these determinations agreed closely with those expected from the elimination of 1 mol. of hydrogen chloride from trichloroethylene. The average experimental values were 0·99 at 444·5°, 1·10 at 425°, and 0·99 at 385°. The measured kinetics were therefore those of the dehydrochlorination of trichloroethylene.

It was soon apparent that the kinetics were complex. The reaction showed an induction period at all temperatures (see Fig. 1). It is unlikely that this arose from a trace impurity acting as an inhibitor because consistent results were obtained with several samples of trichloroethylene over very varying stages of reservoir exhaustion. Even after allowance for the

induction period a graph drawn from the experimental results relating log $d[C_2HCl_3]/dt$ to log $[C_2HCl_3]$ at constant temperature is markedly curved, showing that the reaction was not of constant order throughout its course. At the end of the induction period the order was 2—3, and it rose to a value impossibly high for a single process. The reaction was therefore either proceeding to an equilibrium or it was inhibited by the reaction products. Consistent with either of these hypotheses, it was shown that the reaction was retarded by excess of the reaction products. The possibility of an equilibrium (unlikely from consideration of the long-term hydrogen chloride analyses) may be rejected by considering the effect of propylene upon the kinetics. Propylene acted as a powerful inhibitor, maximum inhibition being reached with about 2 mm. pressure of propylene. It was shown that this maximally inhibited rate was invariant with propylene concentration up to at least 10 mm., and *n*-hexane was found to reduce the rate constant to the same limit. For the inhibited experiments, therefore, an initial propylene pressure of 5 mm. was used. The maximally inhibited non-chain reaction was found to be devoid of induction period and to be of second order. This is illustrated in Fig. 2, which shows experimental results obtained at 410° and 444·5°, and where the full lines are calculated on the assumption that the reaction is of second order. The constancy of the order of this residual reaction (see also Table 1) proves that the dehydrochlorination cannot go to an equilibrium.

TABLE 1.

Temp.	385°	410°	444·5° *a*	444·5° *b*	444·5° *c*	444·5° *p*
10^2k	1·38	5·67	17·0	20·6	20·7	20·8

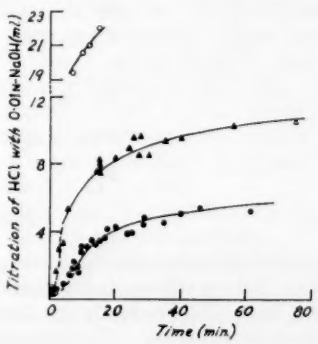
a, p_0 = 18·3 mm. *c*, p_0 = 42·5 mm.
b, p_0 = 28·3 mm. *p*, packed vessel, p_0 = 42·5 mm.

The reaction was also studied in a packed reaction vessel of approx. 11-fold increase in surface/volume ratio over that of the " empty " vessel. The maximally inhibited reaction was independent of surface/volume ratio. The mean observed rate constants are given in Table 1. They may be summarised as $k = 10^{12\cdot08}e^{-42,000/RT}$ sec.$^{-1}$ mole^{-1} l.

The reaction occurring in the presence of 5 mm. of propylene is non-chain in character; it will therefore have no mechanistic interconnection with the suppressible, radical-chain part of

FIG. 3.

○ 444·5°, 42·5 mm. pyrolysed for 40 min. and 33 mm. added in unpacked reactor.
▲ 444·5°, p_0 = 42·5 mm., packed reactor, volume 138 ml.
● 444·5°, p_0 = 16 mm., unpacked reactor, volume 190 ml.



the pyrolysis. Subtraction of the maximally inhibited rate from the uninhibited rate at any particular concentration thus gives the instantaneous rate of the chain decomposition. Trial and error methods showed that this part of the reaction was fitted by an empirical equation, Rate = $k'[C_2HCl_3]^2/[HCl]$, from the end of the induction period as far as reaction has been followed (*ca.* 75% decomposition), implying that the chain reaction was of second order and was inhibited by one of the products. Fig. 3 shows the fit of this equation to some of the results.

Owing to the complicated form of the hydrogen chloride titration *versus* time curves, the runs used for elucidating the kinetics have been started from standard initial concentrations of reactant. The experimental values of k' are given in Table 2. From these results k' =

TABLE 2.

Temp.	385°	410°	425°	444·5°	444·5° *p*
$10^5k'$ (sec.$^{-1}$)	5·0	16·6	33·3	53·3	53·3

$10^{7.52}e^{-35,400/RT}$ (the velocity constant at 444·5° is given 3 times the weight of the others because it is averaged from 3 series of runs differing in initial pressure or surface/volume ratio of the reaction vessel). Table 2 also shows that packing the reaction vessel had no effect upon the chain part of the reaction, so that the whole decomposition was homogeneous.

Some attempts were made to confirm the partial radical nature of trichloroethylene pyrolysis by accelerating the reaction at 425° by the admission of 2 mm. of 1 : 1 : 1-trichloroethane to the reaction vessel 10 sec. before adding 40 mm. of trichloroethylene. Trichloroethane decomposes rapidly at this temperature by a reaction involving chlorine and trichloroethyl radicals (Barton and Onyon, *J. Amer. Chem. Soc.*, 1950, **72**, 988). The titration figures obtained, however, after 10 min. were close to those expected from a sum of the separate decompositions, so that no large amount of induced decomposition of the trichloroethylene was occurring.

The solid product of trichloroethylene pyrolysis, also obtained in small yield from the decomposition of both tetrachloroethanes, was suggested on m. p. evidence by Barton and Howlett (*loc. cit.*) to be hexachlorobenzene. It has now been collected in larger quantity by the use of the flow technique and recrystallised from ethyl acetate as feathery needles (Found : Cl, 74·2%; *M*, 283. Calc. for C_6Cl_6 : Cl, 74·7%; *M*, 285), m. p. 222—223° (lit., m. p., 223—224°). Furthermore, in a dynamic experiment run at 490° with a hot contact time of 2 min., 0·025 mole of crude hexachlorobenzene was obtained concurrently with the production of 0·071 mole of hydrogen chloride.

Discussion

The chain part of the thermal decomposition of trichloroethylene presents certain novel features, *e.g.*, the dependence of the rate upon the square of the reactant concentration is unusual, and this also applies to the definite inhibition by one of the reaction products, and to the pressure dependence of the induction periods (see Fig. 1 and p. 2603). The following alternative reaction schemes, which employ bimolecular steps in the decompositions of small molecules and radicals,* are consistent with the pyrolytic features described above.

$$2C_2HCl_3 \xrightarrow{k_1} Cl + C_2HCl_2 + C_2HCl_3$$

$$\text{or} \xrightarrow{k_1'} HCl + C_2HCl_2 + C_2Cl_3$$

$$Cl + C_2HCl_3 \xrightarrow{k_2} HCl + C_2Cl_3$$

$$C_2HCl_3 + C_2Cl_3 \xrightarrow{k_3} Cl + C_2Cl_2 + C_2HCl_3$$

$$C_2HCl_3 + C_2HCl_2 \xrightarrow{k_4} Cl + C_2HCl + C_2HCl_3$$

$$C_2HCl_3 + Cl + \text{Product} \xrightarrow{k_5} \text{End of chain}$$

$$3C_2Cl_2 \longrightarrow C_6Cl_6 \text{ (mechanism unspecified)}$$

The trichloroethylene merely participates in step 5 for initial stabilisation of the reaction product. Either scheme leads directly to an expression of the type Rate $= d[HCl]/dt = ([C_2HCl_3]^2k_1k_2)/(k_5[\text{Product}])$ (cf. Robb, *Nature*, 1953, **172**, 1055) in agreement with the experimental equation. The expression $d[HCl]/dt = k[C_2HCl_3]^2 + k'[C_2HCl_3]^2/[\text{Product}]$ has been tested against all the experimental results. The full lines in Figs. 1 and 3 are theoretical, being obtained by graphical integration of this last equation, because it is impracticable to use the cumbrous integrated form of the rate equation

$$kt = \frac{A[\text{Product}]_t}{[C_2HCl_3]_t} + \frac{B \ln [C_2HCl_3]_0 (\lambda + [\text{Product}]_t)}{\lambda[C_2HCl_3]_t}$$

where

$$A = \frac{1}{[C_2HCl_3]_0 + \lambda'}, \quad B = -\frac{\lambda}{([C_2HCl_3]_0 + \lambda)^2}, \quad \lambda = k'/k$$

and the subscripts 0 and t have the obvious meaning. The rate equation fits the experimental results over the whole of the pressure range investigated and is still valid in

* We thank the referees for a suggestion which avoids anomalies in our formulation.

the presence of considerable quantities of reaction products (see Fig. 3). As shown by the dynamic experiments, the dichloroacetylene initially produced, rapidly and completely polymerises to hexachlorobenzene (cf. Berthelot and Jungfleisch, *Annalen*, 1870, Suppl. 7, 255; Nicodemus, *J. pr. Chem.*, 1911, **83**, 312; Ott and Dittus, *Ber.*, 1943, **76**, 80). This explains the final fall in pressure towards p_0 found in the static experiments. The degree of inhibition in runs performed in the presence of reaction products from previous experiments was quantitatively consistent with the idea that the concentration of inhibitor was equal to the sum of the old and the new products. As there was no loss of inhibitory efficiency with time, this suggested that the inhibitor was hexachlorobenzene. The overall rate of trichloroethylene decomposition is certainly negligible in comparison with those of the tetrachloroethanes, and further, although the latter are pyrolysed by radical-chain mechanisms, it seems most unlikely from the co-decompositions with 1 : 1 : 1-trichloroethane that the tetrachloroethanes would sensitise the decomposition of trichloroethylene. As with allyl chloride, therefore, trichloroethylene reacts much more slowly than the saturated compound(s) from which it may be derived pyrolytically, a conclusion in agreement with the preliminary findings of Barton and Howlett (*loc. cit.*).

The reaction is also interesting from the point of view of Slater's theory (*loc. cit.*). The pyrolysis of trichloroethylene is the first reported dehydrohalogenation reaction whose homogeneous non-chain mode of reaction is of second-order at a pressure of *ca.* 50 mm. This is in complete agreement with Slater's deduction. As the experimental difficulties attending observation of the pyrolysis of trichloroethylene precluded working at higher pressures, it is intended to carry out such a study with other hexatomic molecules of this type. There is also some evidence that the chain-initiating step is bimolecular rather than unimolecular. As emphasised previously (Barton and Howlett, *J.*, 1951, 2033), the observation of induction periods allows one to decide on some of the more intimate aspects of a reaction mechanism. In all cases of first-order radical-chain dehydrochlorination reactions so far reported the induction periods are independent of the initial pressure to a first approximation. We have applied Howlett's approximate treatment (*Trans. Faraday Soc.*, 1952, **48**, 25; cf. also Benson, *J. Chem. Phys.*, 1952, **20**, 1605) relating the induction period with rate of build-up towards the stationary state, to our theoretical scheme, and to the alternative scheme in which steps 1, 3, and 4 are unimolecular. Thus from our mechanism $[C_2Cl_3] = k_2[Cl]/k_3 = 2k_1k_2[C_2HCl_3]/k_3k_5[\text{Product}]$ in the steady state, and $d[C_2Cl_3]/dt \approx 2k_1[C_2HCl_3]^2$ during the induction period. Therefore induction period $\approx k_2/k_3k_5[C_2HCl_3]'[\text{Product}]'$ where $[C_2HCl_3]'$ and $[\text{Product}]'$ are the concentrations at the end of the induction period when the chain reaction has just reached the steady state. The mechanism following a unimolecular initial step leads by similar reasoning to an induction period of $k_2[C_2HCl_3]'/k_3k_5[\text{Product}]'$.

At 444·5° the induction period found by extrapolating back the full lines of Fig. 3 to zero [Product] are 0·9 min. and 6·2 min. at 42·5 mm. and 16 mm., respectively. Clearly, this rapid inverse dependence of the induction period on the initial pressure is in agreement with the behaviour expected from a bimolecular chain-initiating reaction, and therefore the chain part of the thermal decomposition of trichloroethylene also supports Slater's deduction.

The induction periods associated with chloroethylene pyrolyses generally and other quantitative aspects of their reaction mechanisms will be discussed in a later paper.

We thank Professor D. H. R. Barton for a gift of propylene. The work described in this and the previous paper was carried out during the tenure of a D.S.I.R. maintenance award (A. M. G.) and of an I.C.I. Research Fellowship (K. E. H.).

BEDFORD COLLEGE, LONDON, N.W.1. [*Received, January 30th*, 1954.

The Kinetics of Oxidation by Nitrous Acid and Nitric Acid. Part I. Oxidation of Formic Acid by Nitrous Acid.

By Jean V. L. Longstaff and K. Singer.

[Reprint Order No. 5179.]

The kinetics of the reaction between formic acid and nitrous acid in aqueous sulphuric acid and in aqueous perchloric acid have been investigated. The reaction is approximately of first order with respect to formic acid and of first order with respect to "analytical" nitrous acid at constant initial concentration of analytical nitrous acid. The kinetic data indicate that the rate-determining step is a bimolecular reaction between formic acid and molecular nitrous acid in dilute acid media, and between formic acid and NO^+ or $H_2NO_2^+$ in more acidic media.

Comparatively little work has been reported on the kinetics of oxidation by nitrous acid. Abel and his co-workers recognised the essential rôle of nitrous acid in oxidation by nitric acid and investigated the oxidation of arsenious acid (Abel, Schmid, and Weiss, *Z. physikal. Chem.*, 1930, **147**, 76) and of sulphurous acid (Abel and Proisl, *Monatsh.*, 1935, **66**, 6) by aqueous nitrous acid. They also made a careful study of the kinetics of the reversible self-decomposition of nitrous acid in dilute nitric acid and in other mineral acids (Abel and Schmid, *Z. physikal. Chem.*, 1928, **132**, 55; **134**, 279; Abel, Schmid, and Babad, *ibid.*, 1928, **136**, 55). In dilute mineral acid, nitrous acid disproportionates according to the equation

$$3HNO_2 \rightleftharpoons HNO_3 + 2NO + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In their kinetic work on oxidation by nitrous acid, Abel and his co-workers found it necessary to repress this reaction by shaking the reaction mixture in an atmosphere of nitric oxide in order to obtain reproducible results. Bobtelsky and Kaplan (*Z. anorg. Chem.*, 1930, **189**, 234) found the reaction between potassium iodide and nitrous acid to be of first order with respect to both reactants.

In the present work the oxidation of formic acid by nitrous acid was investigated in aqueous sulphuric acid (0·1—6M), aqueous perchloric acid (1—6M), and in water. The oxidation in aqueous nitric acid is described in Part II (following paper). Concentrations of less than 10^{-2}M-nitrous acid were used and under these conditions the rate of self-decomposition of nitrous acid is slow compared with the rate of oxidation and can be allowed for. All kinetic experiments were carried out at 25°. Dissolved oxygen was initially removed from the reactant solutions and the reaction mixture was screened from light. The course of the reaction was followed by colorimetric estimation of nitrous acid and, in some experiments, also by determination of the amount of carbon dioxide formed by oxidation of formic acid.

The initial concentration of nitrous acid was varied between 10^{-4} and 10^{-2}M and the reaction was followed up to about 70% consumption of the nitrous acid. The initial concentration of formic acid was varied between 0·5M and 1M and did not change measurably during a run. The following features were observed:

(1) The reaction is of first order with respect to the concentration of "analytical" nitrous acid in all runs; typical graphs of ln (HNO_2) against time, from which the first-order velocity constant k can be obtained, are shown in Fig. 1 [(HNO_2) denotes the concentration of "analytical" nitrous acid which comprises all molecular entities which diazotise aromatic amines under the conditions of the colorimetric method of analysis used]. Limited data indicate that in aqueous solution and in up to 4M-aqueous sulphuric acid the reaction is of first order with respect to formic acid (Table 1). In aqueous perchloric acid there are considerable deviations from first-order dependence on formic acid (Table 1), perhaps owing to inaccuracy caused by the subtraction of a relatively large blank decomposition.

TABLE 1.

Expt.	$H{\cdot}CO_2H$, M	10^4k (min.$^{-1}$)	10^4k_b (min.$^{-1}$)	10^4k_c (min.$^{-1}$)	$10^4k_c'$ (min.$^{-1}$ mole^{-1} l.)
		2·8M-H_2SO_4; Initial $(HNO_2) = 1 \times 10^{-3}$M.			
239*a*	0·51	48	14	34	67
239*b*	1·02	92	14	78	76
255	1·31	95	4	91	69
		2·8M-$HClO_4$; Initial $(HNO_2) = 4 \times 10^{-5}$M.			
72	0·22	58	32	26	120
73	0·55	53	25	28	51
74	1·10	119	25	94	85
75	1·65	184	32	152	92

$k = -\mathrm{d}\ln(HNO_2)/\mathrm{d}t$; $k_b = -\mathrm{d}\ln(HNO_2)/\mathrm{d}t$ for blank run; $k_c = k - k_b$; $k_c' = k_c/[H{\cdot}CO_2H]$.

For the reaction between formic acid (1·2M) and nitrous acid in the absence of mineral acid k_c' was equal to 0·0060 (min.$^{-1}$ mole^{-1} l.).

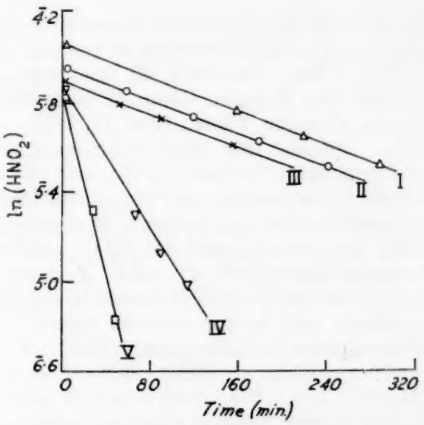


FIG. 1. ln (HNO_2) *plotted against time for experiments in aqueous sulphuric acid.* I, 0·11M; II, 1·0M; III, 2·0M; IV, 3·5M; V, 4·0M.

(2) The rate of the reaction is approximately independent of acidity in media up to 2·5N with respect to H^+ but increases rapidly with acidity above $[H^+] = 3$N (Tables 2 and 3).

TABLE 2. *Experiments in aqueous sulphuric acid.* Initial $(HNO_2) = 1 \times 10^{-3}$M.

$[H_2SO_4]$, M	0·1	1·0	2·0	2·8	3·5	4·0
$10^3k_c'$ (min.$^{-1}$ mole^{-1} l.)	6·0	6·0	5·5	7·2	29·5	101

TABLE 3. *Experiments in aqueous perchloric acid.* Initial $(HNO_2) = 4 \times 10^{-5}$M.

$[HClO_4]$, M	0·1	0·46	0·9	1·9	2·8	3·1	3·9	6·0
$10^3k_c'$ (min.$^{-1}$ mole^{-1} l.)	5·1	4·9	4·9	5·9	8·5	9·0	30·0	67·0

(3) The ratio of amount of carbon dioxide formed to the change in concentration of "analytical" nitrous acid in a given reaction time corrected to allow for the self-decomposition of nitrous acid, $q = [\Delta(CO_2)/\Delta(HNO_2)]_{corr.}$, is approximately -1 in >2·8M-sulphuric acid, and $-0{\cdot}5$ in <2·0M-sulphuric acid (Table 4). In aqueous perchloric acid, $q \approx -0{\cdot}5$ in <1·0M- and ≈ 1—1·5 in >3M-solution.

TABLE 4.

$[H_2SO_4]$, M	0·44	0·55	2·0	2·8	2·8	3·6
$-q$	0·61	0·50	0·68	1·13	1·0	0·97

(4) Although satisfactory first-order constants with respect to "analytical" nitrous acid are obtained in any given run, the velocity constants increase with the initial concentration of nitrous acid (Table 5).

TABLE 5. $[H_2SO_4] = 2{\cdot}8$M.

Initial (HNO_2), M $\times 10^3$	0·7	0·9	2·7	12·6
$10^3k_e'$ (min.$^{-1}$ mole^{-1} l.)	7·6	6·7	11·5	16·5

(5) Formate ion appears to be less reactive than formic acid (see p. 2608).

DISCUSSION

The Course of the Reaction.—The oxidation of formic acid to carbon dioxide may proceed by two one-electron transfers, *e.g.*,

$$HNO_2 + H{\cdot}CO_2H = NO + H_2O + H\dot{C}O{\cdot}O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$
$$H{\cdot}CO{\cdot}O + HNO_2 = NO + H_2O + CO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2b)$$

or by a two-electron transfer,

$$HNO_2 + H{\cdot}CO_2H = HNO + CO_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

with possible further reaction between nitroxyl and formic acid. The presence of H·CO·O radicals and of HNO radicals in reaction mixtures has variously been postulated (Hart, *J. Amer. Chem. Soc.*, 1951, **73**, 68; Style and Ward, *J.*, 1952, 2125; Andrussow, *Ber.*, 1926, **59**, 458; *Z. angew. Chem.*, 1926, **39**, 332; 1935, **48**, 593; Baudisch, *Ber.*, 1921, **54**, 410; Raschig, *Z. angew. Chem.*, 1904, **17**, 1410; Gray and Style, *Trans. Faraday Soc.*, 1952, **48**, 1137). The fact that some reduction of mercuric chloride occurs in mixtures of nitrous and formic acids, but not in either acid alone, affords some evidence for the presence of free radicals in the reaction mixture (cf. Wieland and Zilg, *Annalen*, 1937, **530**, 257).

Possible reduction products of nitrous acid are nitric oxide (Winkler, *Ber.*, 1901, **34**, 1412), hyponitrous acid $(H_2N_2O_2)$, nitrous oxide, and hydroxylamine (cf. Raschig, *Z. angew. Chem.*, 1904, **17**, 1411; *Z. anorg. Chem.*, 1926, **155**, 225). Direct identification of the reduction product proved to be too difficult because of the small initial concentration of nitrous acid in the reaction mixtures. Some indirect evidence, however, may be obtained from the ratio q (see p. 2605). If the final reduction product is nitric oxide, $q = -0{\cdot}5$; reduction to HNO, $H_2N_2O_2$, or N_2O would give $q = -1{\cdot}0$; and reduction to $NH_2{\cdot}OH$, $q = -2{\cdot}0$. The observed values (Table 4) suggest that the final reduction product is nitric oxide in dilute acid media and N_2O, $H_2N_2O_2$, or HNO in stronger acid, but do not permit a distinction between the mechanisms (2*a*), (2*b*), and (3), since HNO formed by (3) could subsequently be oxidised to nitric oxide: $HNO + HNO_2 = 2NO + H_2O$.

The participation of atmospheric oxygen, which was not rigorously excluded during the runs, in the reaction (*e.g.*, by oxidation of nitric oxide) would invalidate deductions based on the observed values of q, but this possibility is discounted for the following reasons. The procedure used led to reproducible results, which would be unlikely unless the reaction involving atmospheric oxygen were to go to completion. It seems unlikely that sufficient oxygen to reoxidise the nitric oxide or nitroxyl would have been available. Moreover the change of $-q$ with increasing acidity from 0·5 to 1·0 implies that oxidation of NO or HNO to NO_2 by oxygen would be complete in the more acidic media and completely absent in less acidic media. This, again, is very improbable, particularly since the solubility of non-polar gases in aqueous solutions is known to decrease with increasing concentration of electrolyte.

The Nature of "Analytical" Nitrous Acid.—The dissociation constant of nitrous acid is $5{\cdot}0 \times 10^{-4}$ at 25° (Schmid, *Angew. Chem.*, 1936, **49**, 378); no appreciable amounts of nitrite ion can therefore be present in the mineral acid media used.

In a recent paper on the kinetics of the gas-phase reaction between N_2O_3, NO, NO_2, and H_2O, Wayne and Yost (*J. Chem. Phys.*, 1950, **18**, 767), using data obtained by Abel and Neusser (*Monatsh.*, 1929, **54**, 855), Verhoek and Daniels (*J. Amer. Chem. Soc.*, 1931, **53**, 1250), and Forsythe and Giauque (*ibid.*, 1942, **64**, 48), have given reliable estimates of the constants for the equilibria $2HNO_2 \rightleftharpoons N_2O_3 + H_2O$, $N_2O_3 \rightleftharpoons NO + NO_2$, and $HNO_2(aq.) \rightleftharpoons HNO_2(g)$. If one assumes that the Bunsen absorption coefficient of NO_2 in water is of the same order of magnitude as that of NO, the constants for the equilibria between NO, NO_2, N_2O_3, and HNO_2 in aqueous solution can be calculated from the gas-

phase equilibrium constants. It is found that in the relevant range the concentrations of NO, NO_2, and N_2O_3 are each less than 1% of the concentration of analytical nitrous acid.

More direct evidence on the nature of analytical nitrous acid was obtained experimentally. According to Abel and his co-workers (*locc. cit.*), the disproportionation of nitrous acid (1) proceeds in two steps :

$$4HNO_2 \rightleftharpoons N_2O_4 + 2NO + H_2O \text{ (rapid)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and

$$N_2O_4 + H_2O \longrightarrow HNO_2 + HNO_3 \text{ (rate-determining)} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

If an appreciable amount of nitrous acid were transformed into dinitrogen tetroxide in the equilibrium (4) the amount of nitrous acid determined by diazotisation would not correspond to the amount of sodium nitrite introduced. No such discrepancy was observed. Further, the ultra-violet absorption spectra of dinitrogen tetroxide in carbon

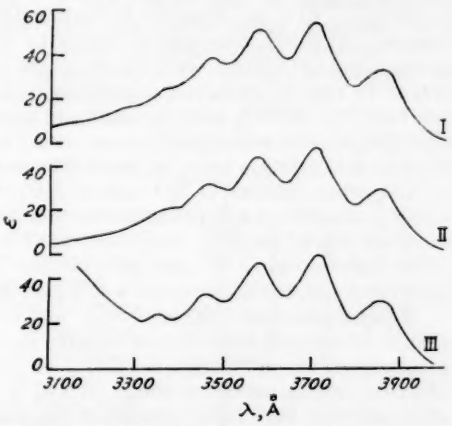


FIG. 2. *Absorption spectrum of "analytical" nitrous acid in different acid media.* I, in 4M-sulphuric acid; II, in 4M-perchloric acid; III, in 0·05M-nitric acid.

tetrachloride and of aqueous acidic solutions of nitrous acid were recorded, and no trace of the absorption band of dinitrogen tetroxide was detected in the nitrous acid solutions. The extinction curves of nitrous acid (0·04M) in 0·05M-HNO_3, 4M-$HClO_4$, and 4M-H_2SO_4 between $\lambda = 3350$ Å and 4000 Å are almost identical (Fig. 2) and similar to the spectrum obtained by Kortüm (*Z. physikal. Chem.*, 1939, **43**, *B*, 418) for nitrous acid dissolved in 0·05N-hydrochloric acid. By comparing the spectra of gaseous mixtures of NO, NO_2, and H_2O, and NO, NO_2, and D_2O, Porter (*J. Chem. Phys.*, 1951, **19**, 1278) has proved conclusively that the four absorption maxima between 3400 Å and 3900 Å are due to molecular nitrous acid.

It is therefore concluded that, in the acid media used in the present work, the bulk of analytical nitrous acid is molecular nitrous acid.

Kinetics of the Reaction.—The first order of the reaction with respect to analytical nitrous acid and to formic acid can be accounted for by a rate-determining step which consists of either (1) a bimolecular reaction between $H{\cdot}CO_2H$ or $H{\cdot}CO{\cdot}O^-$ and HNO_2, or (2) a bimolecular reaction between $H{\cdot}CO_2H$ or $H{\cdot}CO{\cdot}O^-$ and a molecular entity X in equilibrium with molecular nitrous acid in the stoicheiometric ratio 1 : 1. The relevant equilibria known or believed to exist in aqueous solutions of nitrous acid are :

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$HNO_2 + H_3O^+ \rightleftharpoons H_2NO_2^+ + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$H_2NO_2^+ \rightleftharpoons NO^+ + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$NO^+ + NO_2 \rightleftharpoons N_2O_3^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$N_2O_3 \rightleftharpoons NO + NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$2NO_2 \rightleftharpoons N_2O_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

$$N_2O_4 + H_2O \rightleftharpoons HNO_2 + HNO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

The possible oxidants are N_2O_3, $N_2O_3^+$, NO^+, $H_2NO_2^+$, N_2O_4, NO_2, and HNO_2. Of these only those stoicheiometrically related to HNO_2 in the ratio 1 : 1 are admissible on kinetic grounds. N_2O_3 and $N_2O_3^+$ must be excluded for this reason. It may be noted that second-order kinetics with respect to nitrous acid have been reported and attributed to attack by N_2O_3 in a number of reactions (cf. Austin, Hughes, Ingold, and Ridd, *J. Amer. Chem. Soc.*, 1952, **74**, 555; Abel, Schmid, and Weiss, *loc. cit.*). [Abel (*Monatsh.*, 1952, **83**, 1103) has proposed a mechanism for the diazotisation of amines in which attack by N_2O_3 may lead to first-order kinetics under certain conditions; it is considered unlikely that these conditions apply here.]

The concentration of NO_2 is determined by the equilibria (10) and (6); two cases have to be considered: (i) if NO accumulates as a reaction product, then $[NO_2] = K[HNO_2]^2/[NO]$ from (10) and (6) and, since $[HNO_2] \approx (HNO_2)$, $[NO_2]$ is not proportional to (HNO_2); (ii) if NO is not formed by a reaction other than (10), $[NO] = [NO_2] \propto [N_2O_3]^{\frac{1}{2}} \propto (HNO_2)$, and attack by NO_2 would give rise to first order with respect to (HNO_2). NO_2 can, however, be excluded as a possible oxidising agent for the following reasons: (1) if NO_2 dimerises according to (11) to an appreciable extent, $[NO_2]$ will not be proportional to (HNO_2); and (2) the rate of oxidation of formic acid in nitric acid media is similar to that of oxidation in perchloric and sulphuric acid solutions of similar acidity (see Part II). If NO_2 were the oxidising agent, the reaction in nitric acid should be faster than that in other mineral acids since, owing to the equilibrium (12), the ratio $[NO_2]/(HNO_2)$ in nitric acid solution must be larger than in other media.

The concentrations of NO^+ and $H_2NO_2^+$ are proportional to $[HNO_2]$ and $[H^+]$. The velocity constant of a bimolecular reaction between NO^+ or $H_2NO_2^+$ and formic acid would therefore depend on $[H^+]$; such a process cannot be the rate-determining step in media up to 3N with respect to H^+, but participation by NO^+ or $H_2NO_2^+$ may well account for the increase of the velocity constants at higher acidities.

Reaction between NO^+ or $H_2NO_2^+$ and formate ion would lead to the observed order as well as to independence of the velocity constant of acidity, since $[NO^+]$ or $[H_2NO_2^+]$ is proportional to $[H^+]$, and $[H{\cdot}CO{\cdot}O^-]$ to $[H^+]^{-1}$. This would therefore account for the observed rate in media for which $[H^+] \ll 3N$, but it is difficult to reconcile this interpretation with the very rapid increase of the reaction rate at $[H^+] > 3N$. Also, some experimental evidence for the non-reactivity of formate ions towards nitrous acid was obtained by comparing the velocities of the reaction in the following two solutions:

	(HNO_2), M	$[NO_2^-]$, M	$[H{\cdot}CO_2H]$, M.	$[H{\cdot}CO{\cdot}O^-]$, M	$[H^+]$, M	k_e'
(A)	$4{\cdot}11 \times 10^{-4}$	$4{\cdot}67 \times 10^{-4}$	1·2	0·6	$3{\cdot}5 \times 10^{-4}$	0·0012
(B)	$8{\cdot}54 \times 10^{-4}$	$2{\cdot}4 \times 10^{-5}$	1·19	$1{\cdot}45 \times 10^{-2}$	$1{\cdot}45 \times 10^{-2}$	0·0060

The velocity constant in (A) is one-fifth of that in (B). Although this may be due to the lower value of $[H^+]$, or possibly to the increase in $[NO_2^-]$, the result is hardly compatible with the assumption that the formate ion is the reactive entity since its concentration in (A) is approximately 40 times that in (B).

It is therefore concluded that in the acidity range $[H^+] = 0{\cdot}1$—$3{\cdot}0$N, the rate-determining step is a bimolecular reaction between HNO_2 and $H{\cdot}CO_2H$. The rapid increase of the reaction velocity at $[H^+] \approx 3N$ is probably due to the increase in concentration of the more reactive oxidising agents NO^+ or $H_2NO_2^+$ in the more acidic media (an increase in the reactivity of HNO_2 or $H{\cdot}CO_2H$ owing to changes in the medium could hardly account for the magnitude of the observed effect).

Insufficient data were obtained to permit a definite interpretation of the observed dependence of the second-order velocity constant on the initial concentration of nitrous acid, but a possible explanation would be a two-step reaction such as

$$H{\cdot}CO_2H + HNO_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H{\cdot}CO_2H,HNO_2 \xrightarrow{k_2} H{\cdot}CO{\cdot}O + NO + H_2O$$

which might give rise to approximately first order with respect to nitrous acid for moderate changes of concentration, but at sufficiently low concentrations of nitrous acid the first rather than the second step might become rate-determining.

Experimental

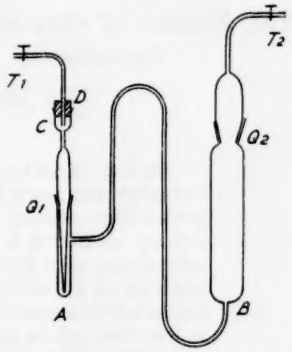
Materials.—" AnalaR " sulphuric acid, perchloric acid, sodium nitrite, and formic acid were used without further purification. Experiments showed that redistillation of the formic acid had no effect on the kinetic results.

Removal of Dissolved Oxygen.—A current of nitrogen, freed from oxygen by a solution of vanadous sulphate in contact with zinc amalgam (Meites and Meites, *Analyt. Chem.*, 1948, **20**, 984) and from carbon dioxide by a solution of barium hydroxide, was passed through the solutions from which the reaction mixture was prepared (*i.e.*, sulphuric or perchloric acid, formic acid, and sodium nitrite solution).

Preparation of the Media.—Sulphuric or perchloric acid solutions were standardised by titration with sodium hydroxide. Media of the required composition were prepared by mixing calculated volumes of sulphuric or perchloric acid, formic acid solution, and sodium nitrite solution in a volumetric flask (100 or 200 ml.) and diluting to the mark with water.

Determination of Nitrite.—The concentration of analytical nitrous acid was determined by the colorimetric method described by Shinn (*Ind. Eng. Chem. Anal.*, 1941, **13**, 33) and modified by Kershaw and Chamberlin (*ibid.*, 1942, **14**, 312), the colour being measured on a Hilger " Spekker " photoelectric absorptiometer. Nitrite concentrations in the range 10^{-3}—10^{-4} mg. of nitrite nitrogen/c.c. are estimated by this method; more concentrated solutions are determined after suitable dilution. The reagents are stable for several weeks, and nitrate and formic acid do not interfere. Calibration curves can be used for several days.

Fig. 3.



Determination of Carbon Dioxide.—The procedure was based on a turbidimetric method (Snell and Snell, " Colorimetric Methods of Analysis," Vol. II, Van Nostrand, New York, 1949). As some of the carbon dioxide formed during the reaction escapes from the liquid phase, the reaction and the subsequent analysis were carried out in glass vessels of the type shown in Fig. 3. The two arms A (a tube 1·5 cm. in diam., 12 cm. long) and B (a tube 2 cm. in diam., 17 cm. long) are joined by a capillary tube. The capacity of the portion of A below the side-arm is a little more than 10 ml. A carries the joint Q_1 which is fitted with an air-leak, a fairly wide capillary extending almost to the bottom of the vessel. The upper end of Q_1 is joined through a short piece of capillary tube to the vessel C (1·5 cm. in diam., 2—3 cm. long). C is closed by a rubber bung D, carrying a tube leading to the nitrogen supply, which is controlled by the tap T_1. The right-hand arm B carries the joint Q_2 connected to the two-way tap T_2, which can be opened to the atmosphere or to a water-pump. The capillary joining A and B is constricted at the junction with B in order to reduce the size of the gas bubbles rising through the barium hydroxide solution and thus to ensure complete absorption of carbon dioxide. A calibration curve was obtained in the following manner:

After passage of nitrogen through the empty vessel for 15 min., Q_2 is removed and 30 ml. of 0·2N-barium hydroxide are transferred to B from a burette; the current of nitrogen is reduced, and Q_2 replaced. Next, Q_1 is removed and the required volume of standard sodium carbonate solution ($\approx 7 \times 10^{-4}$M) is pipetted into A, the nitrogen current is turned off, and Q_1 replaced. D is then removed, about 3 ml. of dilute hydrochloric acid are transferred to C, and D is replaced. A slow current of nitrogen is turned on and gentle suction is applied simultaneously by opening T_2 to the pump. In this way the acid is drawn from C into A and the liberated carbon dioxide is swept into the barium hydroxide solution in B. After 15 min. the contents of B are emptied into a 4-cm. cell, covered by a glass lid, and the optical density of the barium carbonate suspension is measured on the " Spekker " (Wratten neutral filters are used). The optical density seems to be somewhat dependent on the characteristics of the reaction vessel; separate calibration curves for each vessel had therefore to be used; even so, the average agreement between duplicates was only about 7%. Up to $3{\cdot}5 \times 10^{-6}$ mole of carbon dioxide can be estimated by this method.

Kinetic Experiments.—A 200-ml. volumetric flask and five carbon dioxide vessels (Fig. 3) were used in runs in which both nitrous acid and carbon dioxide were determined. Nitrogen was passed through the mineral acid and sodium nitrite solutions for 30 min. At the same time the carbon dioxide vessels were flushed with nitrogen and charged with barium hydroxide

as described above. The joints Q_2 were then replaced by Quickfit stoppers, the taps T_1 closed, and the vessels placed in the thermostat (25°). The calculated volumes of the reactants were mixed in the 200-ml. volumetric flask and placed in the thermostat; 5-ml. portions of the reaction mixture were pipetted rapidly into the arm *A* of each carbon dioxide vessel (opened for this purpose by lifting Q_1). For the nitrite estimation, 5-ml. samples, taken from the 200-ml. flask at suitable intervals, were added to an excess of cooled sodium hydroxide; the resultant solution was almost neutralised with hydrochloric acid and made up to a standard volume. The colorimetric determination of nitrite (p. 2609) was carried out on a suitable aliquot part of this solution.

After corresponding time intervals, carbon dioxide vessels were in turn taken from the thermostat; the reaction was quenched by placing the arm *A* in ice, and carbon dioxide was determined after sweeping the carbon dioxide into the barium hydroxide solution and turbidimetric measurement of the precipitate as described above.

A blank experiment was carried out at the same time: nitrous acid was estimated in samples taken from a solution of the same composition as the reaction mixture but containing no formic acid.

ROYAL HOLLOWAY COLLEGE (UNIVERSITY OF LONDON),
ENGLEFIELD GREEN, SURREY.

[*Received, March 4th* 1954.]

The Kinetics of Oxidation by Nitrous Acid and Nitric Acid. Part II. Oxidation of Formic Acid in Aqueous Nitric Acid.*

By JEAN V. L. LONGSTAFF and K. SINGER.

[Reprint Order No. 5180.]

The rate of oxidation of formic acid in 0·04—18·4M-nitric acid at 25° is of first order with respect to "analytical" nitrous acid and to formic acid. The second-order velocity constant varies with the concentration of nitric acid; a sharp maximum is reached at $[HNO_3] = 12{\cdot}5$M. The kinetic results, in conjunction with evidence derived from ultra-violet absorption spectra of solutions of nitrous acid in nitric acid, indicate that the rate-determining step is a bimolecular reaction between formic acid and molecular nitrous acid in less than ≈2·5M-nitric acid, and between formic acid and NO^+ at higher concentrations of nitric acid.

THERE are but few reports on the kinetics of oxidation by aqueous nitric acid. The only careful investigation—apart from an early paper by Eckstädt (*Z. anorg. Chem.*, 1902, **29**, 51) on the oxidation of iodide—appears to be that of Abel, Schmid, and Weiss (*Z. physikal. Chem.*, 1930, *A*, **147**, 69) on the oxidation of arsenious acid in up to 2·6M-nitric acid containing nitrous acid, which is of first order with respect to arsenious acid and of second order with respect to nitrous acid. The authors interpret the order by assuming N_2O_3 (in equilibrium with nitrous acid) to be the oxidising agent. Abel, Schmid, and Babad (*ibid.*, 1928, **136**, 135, 419) also investigated the kinetics and equilibria of the reactions of nitrous acid and of oxides of nitrogen in aqueous nitric acid.

In the present work the oxidation of formic acid in aqueous nitric acid (0·04—18·4M) at 25° was followed by determination of the change of concentration of "analytical" nitrous acid [denoted by (HNO_2) and defined as in Part I], and, in some experiments, also by determination of the amount of carbon dioxide formed. In <1M-nitric acid, nitrous acid (<0·04M) decomposes slowly and a correction had to be made by running blank experiments; this was not necessary in >1M-nitric acid. The principal features of the reaction are:

(1) No reaction is detected in the absence of nitrous acid.

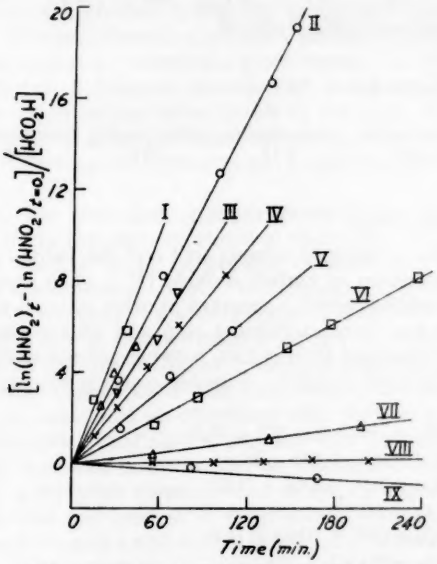
(2) The concentration of analytical nitrous acid increases autocatalytically in reaction mixtures containing 1M-nitric acid, it is approximately constant in 1M-nitric acid, and decreases in <1M-nitric acid solutions (Fig. 1).

* Part I, preceding paper.

(3) The change of concentration of analytical nitrous acid is of first order over the range 10^{-4}—10^{-2}M, and that of formic acid is of first order over the range 0·2—1·2M. Values of the velocity constants $k' = \{d \ln (HNO_2)/dt\}/[H{\cdot}CO_2H]$ (obtained from the slopes of the linear plots of $\ln (HNO_2)$ against time) for three concentrations of nitric acid are given in Table 1. Duplicates are included in order to illustrate the reproducibility of the results.

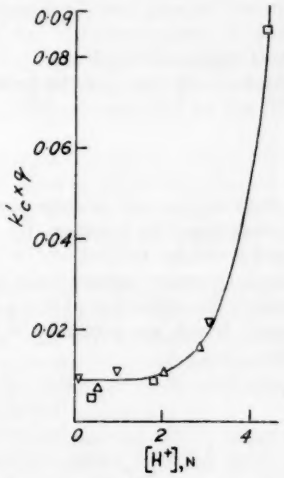
(4) The second-order velocity constant increases slowly between $[HNO_3] = 1$M and 4M, it increases rapidly (19-fold) between $[HNO_3] = 4$M and 12·5M, and decreases (5-fold)

FIG. 1. $[\ln (HNO_2)_t - \ln (HNO_2)_{t=0}]/[H{\cdot}CO_2H]$ *plotted against time for experiments in nitric acid.*



Acid strengths are: I, 12·5M; II, 11·1M *and* 14·1M; III, 15M; IV, 16M; V, 8·2M; VI, 18·4M; VII, 3·8M; VIII, 1·0M; IX, 0·1M.

FIG. 2. *The velocity constant for the formation of carbon dioxide plotted against* $[H^+]$ *in different acid media.*



□ = HNO_3,aq.
△ = H_2SO_4,sq.
▽ = $HClO_4$,aq.

between $[HNO_3] = 12{\cdot}5$M and 18·4M. In <1M-nitric acid the velocity constant is negative (*i.e.*, the concentration of nitrous acid decreases during the reaction) (Table 2, Figs. 1 and 4). The variation of the velocity constant for the formation of carbon dioxide ($k' \times q$) in

TABLE 1.

$[HNO_3]$ = 7·9 M.								
$[H{\cdot}CO_2H]$, M	0·25	0·25	0·61	0·61	1·21	1·21		
k' (min.$^{-1}$ mole^{-1} l.)	0·047	0·047	0·047	0·046	0·056	0·054		
$[HNO_3]$ = 11·0 M.								
$[H{\cdot}CO_2H]$, M	0·24	0·25	0·26	0·61	0·61	1·19	1·22	
k' (min.$^{-1}$ mole^{-1} l.)	0·132	0·133	0·138	0·131	0·139	0·151	0·139	
$[HNO_3]$ = 12·5 M.								
$[H{\cdot}CO_2H]$, M	0·21	0·22	0·25	0·53	0·53	0·62	0·65	1·13
k' (min.$^{-1}$ mole^{-1} l.)	0·157	0·146	0·148	0·155	0·149	0·158	0·137	0·148

TABLE 2.

$[HNO_3]$, M	0·1	0·44	2·0	3·8	4·2	7·9	9·6	11·0
$k' \times 10^2$	−0·4	−0·8	0·59	0·78	0·85	4·7	9·0	13·0
$[HNO_3]$, M	12·3	13·3	14·1	15·0	16·0	16·7	18·4	
$k' \times 10^2$	16·0	14·8	12·7	10·9	8·2	7·0	3·5	

[The two negative values for k' are not strictly comparable because the initial concentration of nitrous acid in the two experiments was different (see Part I).]

1—6M-aqueous nitric acid (*i.e.*, ≈1—4N with respect to $[H^+]$) is quantitatively similar to the change of the corresponding velocity constant ($k_c' \times q$) for the reaction between nitrous acid and formic acid in aqueous sulphuric and perchloric acids in the same range of acidity (Fig. 2). (Values of $k_c' \times q$ are inaccurate owing to the large experimental error in the determination of CO_2.)

(5) The ratio of the amount of carbon dioxide formed to the change of concentration of analytical nitrous acid, $q = \Delta(CO_2)/\Delta(HNO_2)$, varies with the concentration of nitric acid (Table 3).

TABLE 3.

$[HNO_3]$, M	0·04	0·44	1·0	2·0	4·2	8·9	9·4	13·9	15·1
q	−0·5	−0·7	∞	1·3	1·1	1·1	0·9	0·9	0·9

(6) The reaction is accelerated by addition of salts (Table 4).

TABLE 4.

$[H{\cdot}CO_2H] = 0{\cdot}52$M, $[HNO_3] = 3{\cdot}8$M.

Salt added	(None)	1·71M-$NaNO_3$	3·0M-$NaNO_3$	1·13M-Na_2SO_4	2·25M-Na_2SO_4	2·0M-$NaClO_4$
$k' \times 10^2$ ...	0·78	1·24	1·95	1·17	1·97	2·60

DISCUSSION

No reaction appears to take place in the absence of nitrous acid and the value of the second-order velocity constant for the formation of carbon dioxide ($k' \times q$) in aqueous nitric acid is similar to that of the corresponding velocity constant in other mineral acids. Nitric acid therefore cannot take part in the rate-determining step and its function is, presumably, the oxidation of the initial products of the reaction between nitrous acid and formic acid, which are probably NO and H·CO·O or HNO. Possible reaction schemes are therefore :

$$H{\cdot}CO_2H + HNO_2 = H{\cdot}CO{\cdot}O + NO + H_2O \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$H{\cdot}CO{\cdot}O + HNO_2 = CO_2 + NO + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

$$H{\cdot}CO{\cdot}O + HNO_3 = NO_2 + CO_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (2b)$$

$$2NO + HNO_3 + H_2O = 3HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

or

$$H{\cdot}CO_2H + HNO_2 = CO_2 + HNO + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$HNO + HNO_3 = 2HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

If nitric oxide is the initial reduction product, and if α is the fraction of nitric oxide reoxidised according to (3), $q = \Delta(CO_2)/\Delta(HNO_2) = 1/(3\alpha - 2)$. The rate of oxidation of nitric oxide by nitric acid is known to increase with the concentrations of nitric acid (*idem, ibid.*). If the limiting value $\alpha = 0$ were attained in very dilute nitric acid, q should be −0·5; and as α increases from 0 to 1, q should change from −0·5 through ∞ to 1. The experimentally observed values of q do in fact exhibit this behaviour (Table 3). Qualitatively similar results would be observed if HNO were the initial reaction product, but in this case the limiting value [pertaining to no reoxidation of HNO by (5)] would be −1·0. The experimental results therefore indicate that the reaction proceeds by (1), (2*a*), and (3), although initial reduction of nitrous acid to HNO, followed by partial reoxidation of the latter to nitrous acid, cannot be definitely excluded. Measurement of the velocity of oxidation of nitric oxide by nitric acid of different concentrations would permit a more definite distinction between the alternative reaction schemes. The kinetic results for the reaction (3) obtained by Abel, Schmid, and Babad (*loc. cit.*) cannot be used here for quantitative calculations because their experimental conditions were too different.

The Nature of Analytical Nitrous Acid in Nitric Acid.—Equilibria involving aqueous nitric acid, nitrous acid, and oxides of nitrogen have been studied mainly by determining the composition of the vapour phase above the solution (Sanfourche, *Ann. Chim.*, 1924, **10**, 1; Burdick and Freed, *J. Amer. Chem. Soc.*, 1921, **43**, 518; Abel, Schmid, and Stein, *Z. Elektrochem.*, 1930, **36**, 692) and by E.M.F. measurements (Pick, *Z. Elektrochem.*, 1920, **26**, 193; Vetter, *Z. anorg. Chem.*, 1949, **260**, 246). Apart from Vetter, these authors are in

general agreement about the qualitative features: in very dilute nitric acid, nitrous acid decomposes according to $3HNO_2 \rightleftharpoons HNO_3 + 2NO + H_2O$, the equilibrium being established only if a constant pressure of nitric oxide is maintained above the solution; in moderately concentrated nitric acid, nitrous acid is largely dehydrated, $2HNO_2 \rightleftharpoons N_2O_3 + H_2O$; and in concentrated nitric acid, nitrous acid is converted into dinitrogen tetroxide: $HNO_2 + HNO_3 \rightleftharpoons N_2O_4 + H_2O$. Oxygen compounds of tervalent nitrogen are stated to be virtually absent in nitric acid of greater concentration than ≈11M (Sanfourche, *loc. cit.*; Foerster and Koch, *Z. angew. Chem.*, 1908, **21**, 2171).

Ultra-violet absorption spectra of analytical nitrous acid in nitric acid of different concentrations were measured and are shown in Fig. 3. In up to 6M-nitric acid the extinction curve between $\lambda = 3350$ Å and 4000 Å is quantitatively that of molecular nitrous acid (cf. Part I, Fig. 2); as the concentration of nitric acid is increased from 6 to 14M, the characteristic absorption bands of HNO_2 give way to a strong general absorption which increases towards the short waves. In 15·7M-nitric acid, this general absorption is about 1·5—2 times as intense but otherwise similar to the absorption of dinitrogen tetroxide in carbon tetrachloride in the same region (Fig. 3). Unfortunately, the strong absorption of nitric acid made measurements at $\lambda < 3500$ Å impossible. It seems probable that the strong absorption in nitric acid is caused by dinitrogen tetroxide for the following reasons:

(1) The good first-order dependence over a considerable range of (HNO_2) indicates that at the low concentrations of analytical nitrous acid used in these experiments, only a small fraction could be present as dinitrogen trioxide. This is supported by approximate calculations of the equilibrium $N_2O_3 + H_2O \rightleftharpoons 2HNO_2$ in aqueous solution (J. V. L. Longstaff, Thesis, London, 1953).

(2) There is strong evidence for the formation of molecular compounds between N_2O_4 and HNO_3 in concentrated nitric acid (Bousfield, *J.*, 1919, **115**, 48; Klemenc and Rupp, *Z. anorg. Chem.*, 1930, **194**, 65); this could easily account for enhanced absorption of N_2O_4 in nitric acid (as compared with N_2O_4 in carbon tetrachloride) and for the fact that the absorption continues to increase with increasing concentration of nitric acid above 14M, which cannot be accounted for by further conversion of HNO_2 into N_2O_4.

It is therefore assumed that analytical nitrous acid is present as HNO_2 in up to 6M-nitric acid and that it is progressively converted mainly into N_2O_4 (and NO_2) as the concentration of nitric acid is increased. Since all traces of the HNO_2 absorption maxima have disappeared in 13—14M-nitric acid, it is concluded that conversion into N_2O_4 is complete at this concentration. A rough estimate for the ratio $[N_2O_4]/(HNO_2)$ in different media can be obtained from the prominence of the inflexion of the curve caused by the absorption bands of HNO_2 (Fig. 3). In order to avoid systematic errors in calculations based on these values, two smooth curves were drawn as closely as possible through the estimated lower and upper limits of the ratio $[N_2O_4]/(HNO_2)$, shown in Table 5. The

TABLE 5.

$[HNO_3]$, M ...	3·75	6·2	8·6	10·4	12·3	12·9	14·0
$[N_2O_4]/(HNO_2)$	0	0·01—0·05	0·10—0·15	0·4—0·6	0·85—0·95	0·93—1·00	1·00

curves were used to calculate upper and lower limits of $[N_2O_4]/(HNO_2)$ for any concentration of nitric acid between 6 and 14M.

Kinetics.—The following equilibria (not all of which are independent of each other) are known or assumed to exist in aqueous nitric acid containing analytical nitrous acid (cf. Abel, Schmid, and Stein, *loc. cit.*; Goulden and Millen, *J.*, 1950, 2620; Hughes, Ingold, and Reed, *J.*, 1950, 2430):

$$H_2O + HNO_3 \rightleftharpoons H_3O^+ + NO_3^- \quad (7)$$
$$HNO_2 + HNO_3 \rightleftharpoons N_2O_4 + H_2O \quad (8)$$
$$N_2O_4 \rightleftharpoons NO^+ + NO_3^- \quad (9)$$
$$HNO_2 + H_3O^+ \rightleftharpoons H_2NO_2^+ + H_2O \quad (10)$$
$$H_2NO_2^+ \rightleftharpoons NO^+ + H_2O \quad (11)$$
$$2HNO_2 \rightleftharpoons H_2O + N_2O_3 \quad (12)$$
$$N_2O_3 \rightleftharpoons NO + NO_2 \quad (12a)$$
$$N_2O_4 \rightleftharpoons 2NO_2 \quad (13)$$
$$NO^+ + NO_2 \rightleftharpoons N_2O_3^+ \quad (14)$$

The entities which may be regarded as possible oxidising agents are therefore HNO_2, NO^+, $H_2NO_2^+$, $N_2O_3^+$, N_2O_3, N_2O_4, NO_2. Attack by N_2O_3 or $N_2O_3^+$ would not lead to the observed first order with respect to analytical nitrous acid.

A rate-determining step involving N_2O_4 would be compatible with the observed order in concentrated nitric acid, where $(HNO_2) \propto [N_2O_4]$ but would lead to second order with respect to (HNO_2) in dilute nitric acid [where N_2O_4 is formed by (13), (12*a*), and (12)]. Attack by NO_2 might lead to first order with respect to (HNO_2) in dilute nitric acid (if no NO accumulates in the reaction mixture; see Part I) and to the order $\frac{1}{2}$ in concentrated nitric acid. It would therefore seem possible that the effective oxidising agents in dilute and in concentrated nitric acid are NO_2 and N_2O_4, respectively. No evidence of a mixed order at intermediate concentrations of nitric acid was, however, observed. Further evidence against the reactivity of N_2O_4 or NO_2 is provided by the similar increase of the rate of the reaction with acidity in nitric acid and in other mineral acids (Fig. 2) although

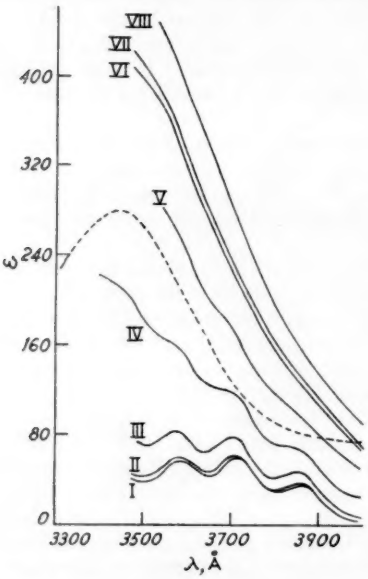


FIG. 3. *Absorption spectra of "analytical" nitrous acid in nitric acid:* I, 3·75M; II, 6·2M; III, 8·2M; IV, 10·4M; V, 12·3M; VI, 12·9M; VII, 13·0M; VIII, 18·7M.

– – – – Absorption spectrum of dinitrogen tetroxide in carbon tetrachloride.

the concentration of N_2O_4 and NO_2 must be greater in nitric acid because of (8). Comparison of the absorption spectra of analytical nitrous acid in >6M-aqueous nitric and other aqueous mineral acids of similar strength shows that the concentration of N_2O_4 is larger in the nitric acid media (Fig. 3 and Part I, Fig. 2).

The remaining entities, NO^+, $H_2NO_2^+$, and HNO_2, would give rise to first order with respect to (HNO_2).

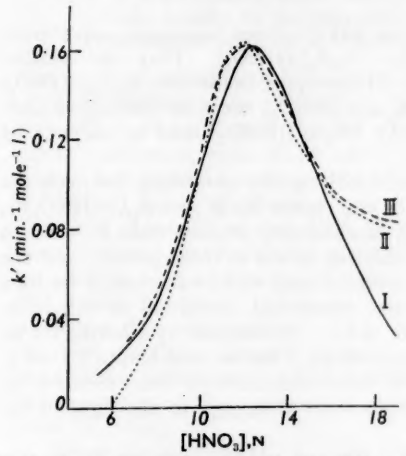
The slow increase of the reaction velocity with hydrogen-ion concentration in <2·5M-nitric acid excludes rate-determining steps involving NO^+ or $H_2NO_2^+$ and it is therefore concluded that in these media the rate-determining step is a bimolecular reaction between HNO_2 and $H{\cdot}CO_2H$ (see also Part I, p. 2604).

The 19-fold change of the velocity constant between 4 and 18M-nitric acid seems too great to be accounted for by a possible change of reactivity of HNO_2 (caused by solvent effects) and must be attributed to the appearance of a more reactive entity. The similar increase of the velocity of oxidation with acidity in nitric, sulphuric, and perchloric acids (Fig. 2) at $[H^+] > 2{\cdot}5$M, and the decrease of the concentration of HNO_2 in >6M-nitric acid, indicate that NO^+ and $H_2NO_2^+$ are, respectively, the principal oxidising agents in these solutions.

If this is so, the variation of the velocity constant in 4—18M-nitric acid (Fig. 4) should

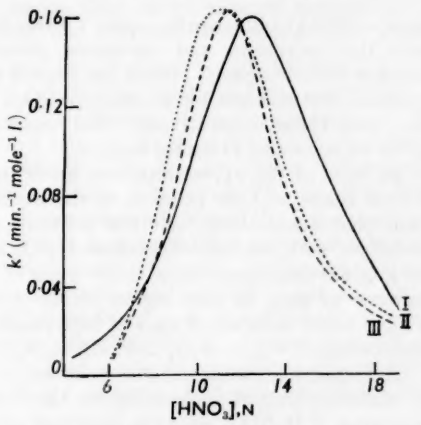
be related to a similar variation of $[NO^+]$ or $[H_2NO_2^+]$. Expressions for the activities of NO^+ and $H_2NO_2^+$ in terms of the activities of HNO_2 and HNO_3 and the equilibrium constants for (7)—(11) can easily be derived (J. V. L. Longstaff, Thesis, London, 1953). The formulæ which are not likely to be seriously affected by the fact that (12), (12*a*), (13), and (14) are disregarded show qualitatively that a_{NO^+} and $a_{H_2NO_2^+}$ tend to zero for both small and large concentrations of nitric acid and must consequently pass through a maximum at some intermediate concentration. Information about the equilibrium constants and activity coefficients necessary for the evaluation of these formulæ is not available. The following features, however, emerge from qualitative considerations: Owing to the operation of the equilibria (10) and (11) [or (10), (8), and (9)] the concentrations of NO^+ and $H_2NO_2^+$ increase with acidity at low concentrations of nitric acid. Since the activity of nitric acid increases more rapidly than the activities of NO_3^- and H_3O^+, the consumption of HNO_2 by the continuing movement of (8) to the right causes

FIG. 4. *Comparison between the observed variation of the velocity constant (k') and of the calculated activity of* NO^+ *with* $[HNO_3]$.



I, k'; II, const. a_{NO^+} (lower limit); III, const. a_{NO^+} (upper limit).

FIG. 5. *Comparison between the observed variation of the velocity constant (k') and of the calculated activity of* $H_2NO_2^+$ *with* $[HNO_3]$.



I, k'; III, const. $a_{H_2NO_2^+}$ (lower limit); II, const. $a_{H_2NO_2^+}$ (upper limit).

(10) to shift to the left. The conversion of HNO_2 into N_2O_4 affects the concentration of NO^+ through (9) and (11) in opposite ways; $[NO^+]$, however, eventually decreases owing to the repression of the dissociation of N_2O_4 by the continued increase of the activity of NO_3^-.

A semiquantitative calculation of the variation of the activities of NO^+ and $H_2NO_2^+$ with $[HNO_3]$ for a given value of (HNO_2) can be carried out by means of: (1) the relations $a_{NO^+} = K_1 a_{N_2O_4}/a_{NO_3^-}$; $a_{H_2NO_2^+} = K_2 a_{NO^+} a_{H_2O}$; (2) the partial pressures of HNO_3 and H_2O above aqueous nitric acid at 25° [obtained by interpolation from Klemenc and Nagel's data (*Z. anorg. Chem.*, 1928, **155**, 257); Wilson and Miles's more recent results (*Trans. Faraday Soc.*, 1940, **36**, 356) could only have been used after some rather inaccurate extrapolation]; and (3) the approximate values for $[N_2O_4]/(HNO_2)$ estimated from the ultra-violet absorption spectra.

Since $a_{H_3O^+} \cdot a_{NO_3^-} \propto a_{H_2O} \cdot a_{HNO_3} \propto p_{HNO_3} \cdot p_{H_2O}$ (where p_{HNO_3} and p_{H_2O} are the partial vapour pressures), the usual (admittedly dubious) assumption $a_{NO_3^-} = a_{H_3O^+}$ leads to $a_{NO_3^-} = a_{H_3O^+} \propto (p_{H_2O} \cdot p_{HNO_3})^{\frac{1}{2}}$.

If it is further assumed that the activity coefficient $f_{N_2O_4}$ does not vary rapidly with $[HNO_3]$, $a_{N_2O_4}$ may be replaced by $[N_2O_4]$ (estimated spectroscopically). Apart from a constant factor, values of $a_{NO^+}/(HNO_2)$ and $a_{H_2NO_2^+}/(HNO_2)$ can be calculated in this way.

To facilitate comparison between the variation of the velocity constant, on the one hand, and $a_{NO^+}/(HNO_2)$ and $a_{H_2NO_2^+}/(HNO_2)$, on the other, with the concentration of nitric acid, the constant factors were adjusted so as to make the maxima of k', $a_{NO^+}/(HNO_2)$, and

TABLE 6.

	Const. $a_{NO^+}/(HNO_2)$		Const. $a_{H_2NO_2^+}/(HNO_2)$	
(HNO_3), M	lower limit	upper limit	lower limit	upper limit
6·2	2·5	4·6	0·5	0·8
8·6	5·1	6·5	7·6	9·6
10·4	12·0	13·9	14·0	16·1
11·3	15·7	15·5	16·4	16·4
12·3	15·7	16·2	14·5	15·0
12·7	—	16·0	—	13·7
12·9	14·8	15·6	12·5	13·0
13·0	14·8	—	12·1	—
14·0	—	13·1	—	9·2
15·0	10·5	11·3	6·3	6·8
16·0	8·7	9·4	4·5	4·8
17·0	8·3	8·9	3·6	3·9
18·0	7·8	8·5	2·8	3·1

$a_{H_2NO_2^+}/(HNO_2)$ numerically equal. Table 6 contains sets of values calculated respectively from the maximum and minimum estimates for $[N_2O_4]/(HNO_2)$. They are plotted together with k' against $[HNO_3]$ in Figs. 4 and 5. If the upper limits for $[N_2O_4]/(HNO_2)$ are used, the maxima for k', $a_{NO^+}/(HNO_2)$, and $a_{H_2NO_2^+}/(HNO_2)$ occur at $[HNO_3] = 12{\cdot}5$, 12·1, and 11·3M, respectively. The lower limits for $[N_2O_4]/(HNO_2)$ lead to maxima at 12·1M for a_{NO^+} and 11·6M for $a_{H_2NO^+}$.

In view of the approximations made in the calculations, the agreement between the general shape and the position of the maximum of the curves for k' and $a_{NO^+}/(HNO_2)$ is considered satisfactory. At low acidities a_{NO^+} is considerably smaller than k'; this is consistent with the hypothesis that HNO_2 is the oxidising entity in these media; and the too gradual decrease of a_{NO^+} to the right of the maximum may well be accounted for by a decrease of $a_{N_2O_4}$ in this region owing to molecular compound formation or solvation. A more rapid decrease of a_{NO^+} at high acidities can, in fact, be obtained by allowing for an equilibrium $HNO_3 + N_2O_4 \rightleftharpoons HNO_3,N_2O_4$ (postulated by Klemenc and Rupp, *loc. cit.*).

Agreement between the curves for $a_{H_2NO_2^+}$ and k' is less satisfactory; there seems to be no plausible way of accounting for the too rapid decrease of $a_{H_2NO_2^+}$ to the right of the maximum if $H_2NO_2^+$ were the oxidising entity.

It is therefore probable that the rate-determining step consists of a bimolecular reaction between HNO_2 and formic acid in 0·1—2·5M-nitric acid, and mainly between NO^+ and formic acid at higher concentrations in up to 18M-nitric acid.

Salt Effects.—The acceleration of the reaction by added salts (Table 4) is probably due to the increase of the concentration of charged entities NO^+, $H_2NO_2^+$, and to an increase of activity of non-polar entities (HNO_2) with increasing ionic strength. The accelerating effect of added nitrate is perhaps unexpected because of the equilibrium $NO^+ + NO_3^- \rightleftharpoons N_2O_4$. However, the experiment was carried out in 3·8M-nitric acid where the concentration of dinitrogen tetroxide is very small, and it is conceivable that in this medium the general salt effect and the effect on the equilibrium (8) (shift to the right) might outweigh the effect caused by the repression of the dissociation of dinitrogen tetroxide by nitrate ion.

Experimental.—The experimental procedures were as described in Part I. Nitric acid was freed from nitrous acid by passage of a current of carbon dioxide or nitrogen for 30 min. in the dark. The concentration of analytical nitrous acid can thus be reduced to 1×10^{-5}M which is sufficient to ensure convenient reaction times in >6M-nitric acid without the addition of sodium nitrite.

Ultra-violet spectra were recorded with a Hilger Uvispek spectrograph in 1-cm. cells. Extinction curves of nitrous acid in nitric acid of different concentrations were measured with nitric acid of the appropriate strength in the solvent cell. The extinction curves in >3M-nitric acid did not change noticeably during the recording of the spectrum (1—2 hr.).

The dinitrogen tetroxide solution was prepared by heating " AnalaR " lead nitrate and by passing the vapour through phosphoric oxide into carbon tetrachloride dried with phosphoric oxide.

We are grateful to Prof. Gwyn Williams for his interest in this work, and we thank the Department of Scientific and Industrial Research for a maintenance grant (to J. V. L. L.). We acknowledge financial assistance from Imperial Chemical Industries Limited and from the Central Research Fund of the University of London.

ROYAL HOLLOWAY COLLEGE (UNIVERSITY OF LONDON),
ENGLEFIELD GREEN, SURREY.

[*Received, March 4th*, 1954.]

Perhydroindanes. Part IV. Some 1-Substituted Hexahydroindanes.*

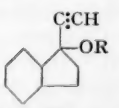
By L. E. COLES, W. H. LINNELL, DAVID W. MATHIESON, and A. S. SHOUKRI.

[Reprint Order No. 5196.]

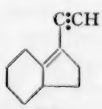
The action of formic acid on 1-ethynylhexahydroindan-1-ol (I; R = H) leads mainly to the non-conjugated ketone (III*a* or *b*). Several bicyclic analogues of cortical hormones, *e.g.*, (VIII) and (IX) have been synthesised.

THE ready availability of hexahydroindanone and hence of 1-ethynylhexahydroindan-1-ol prompted investigation of the hydration of the triple bond under various conditions. It was hoped to synthesise thereby some bicyclic analogues of cortical hormones. The direct addition of water to an acetylenic alcohol of type (I; R = H) might be expected to lead to a pinacol rearrangement with the production of a decalol—this is well known in the steroid series (cf. Shoppee and Prins, *Helv. Chim. Acta*, 1943, **26**, 185, 201, 1004; Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3484). Under the conditions of the Rupe rearrangement, however, the initial step of dehydration to the conjugated vinyl acetylene is followed by addition of the elements of water to the triple bond (Hennion, Davis, and Maloney, *ibid.*, 1949, **71**, 2813): under such conditions rearrangement cannot occur and an $\alpha\beta$-unsaturated ketone results. Thus from ethynyl*cyclo*pentanol, 1-acetyl*cyclo*pentene is obtained (Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 1827). In one recorded case the action of formic acid on 17-ethynyltestosterone led to the corresponding Δ^{16}-compound by elimination of the elements of water (Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, 1938, **71**, 1024).

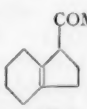
When the alcohol (I; R = H) was refluxed for 45 minutes with 90% formic acid, approximately 50% of a colourless oil was produced consisting mainly of 3-ethynyl-2 : 4 : 5 : 6 : 7 : 8-hexahydroindene (II) with a small amount of an unsaturated conjugated carbonyl component. For identification, the alcohol (I; R = H) was dehydrated with phosphorus oxychloride to give an unequivocal sample of the hydrocarbon (II). This



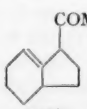
(I)



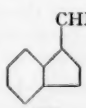
(II)



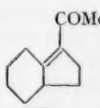
(III*a*)



(III*b*)



(IV)



(V)

suggested formulation instead of the alternative with a 2 : 3-double bond, is discussed below. The product (II) was rather unstable and on distillation polymerised appreciably, which explains the low yields obtained. When the reflux period with formic acid was increased to 2½ hr., a carbonyl component was isolated as its semicarbazone in 16—20% yield. It was tentatively formulated as 1-acetyl-4 : 5 : 6 : 7(or 4 : 5 : 6 : 9)-tetrahydroindane (III) because of the analysis, uptake of 1 mol. of hydrogen on catalytic hydrogenation, and absence of evidence of conjugation in the ultra-violet absorption spectrum of the ketone and its semicarbazone. The arrangement of the carbon skeleton was confirmed by hydrogenation to the saturated ketone whence lithium aluminium hydride yielded the

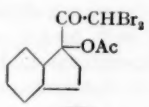
* Part III, *J.*, 1953, 3251.

secondary alcohol (IV). Ketone and alcohol proved identical with samples obtained by the following reactions, X·CO_2H ⟶ X·COMe ⟶ X·CHMe·OH (IV) (X = *cis*-hexahydro-1-indane residue).

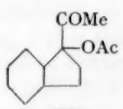
The conjugated ketone (V) was smoothly obtained by addition of aniline to the acetylene (II) in presence of mercuric chloride, followed by hydrolysis of the anil (cf. Stavely, *J. Amer. Chem. Soc.*, 1941, **62**, 3127). Reduction again gave *cis*-1-acetylhexahydroindane. The position of maximum light absorption for the unsaturated ketone (253 mμ) is in agreement with structure (V): the observed bathochromic shift of 15 mμ between 1-acetyl*cyclo*hexene ($\lambda_{max.}$ 232 mμ) and 1-acetyl-2-methyl*cyclo*hexene ($\lambda_{max.}$ 247 mμ) (Heilbron, Jones, Toogood, and Weedon, *loc. cit.*; Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890) is the same as that observed on comparing (V) with the nearest analogue, 1-acetyl*cyclo*pentene ($\lambda_{max.}$ 239 mμ). Similar conclusions as to the position of the double bond in the hydrocarbon (II) are reached by comparing its spectrum ($\lambda_{max.}$ 234 mμ) with that of 1-ethynyl*cyclo*pentene (227 mμ). The observed bathochromic shift is in agreement with that noted on passing from 1-ethynyl*cyclo*hexene ($\lambda_{max.}$ 223 mμ) to 1-ethynyl-2-methyl*cyclo*hexene ($\lambda_{max.}$ 229 mμ) (Milas, McDonald, and Black, *J. Amer. Chem. Soc.*, 1948, **70**, 1831). Since structures (II) and (V) are thus indicated, it follows that (III*a* or *b*) is the most probable structures for the non-conjugated ketone isolated from the Rupe rearrangement. The conjugated and the non-conjugated ketones (V) and (III) provided an interesting comparison in rates of hydrogenation. Under identical conditions with a palladium catalyst in ethanol, that of (V) was ten times more rapid than that of (III). Whether this is an effect of conjugation as in (V), or of steric hindrance about the double bond and therefore indicating (III*a*) rather than (III*b*) for the non-conjugated ketone, is not known. The suggested sequence of the steps during treatment with formic acid, *viz.*, (I) ⟶ (II) ⟶ (V) ⟶ (III) is in line with previous observations. Thus the initial step in a Rupe rearrangement has been shown to be dehydration to produce a conjugated vinylacetylene (Hennion, Davis, and Maloney, *loc. cit.*). The position of equilibrium for the unsaturated ketones Me·CH_2·CMe:CMe·COMe and Me·CH:CMe·CHMe·COMe has been shown to be 83% in favour of the βγ-isomer (Kon, Abbott, and Satchell, *J.*, 1928, 2514). These are structurally analogous to the present case. It has been reported moreover (Takeshima, *J. Amer. Chem. Soc.*, 1953, **75**, 330) that rearrangement of 3 : 4-dimethylhex-1-yn-3-ol with formic acid gives mainly the βγ-isomer, in agreement with the observed position of equilibrium.

Even samples of non-conjugated ketone (III) purified *via* the semicarbazone showed slight absorption at 250 mμ indicative of an amount of contamination by the αβ-isomer estimated to be about 18% : in conformity there was residual absorption at 260—265 mμ by the semicarbazone.

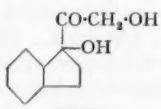
With the failure of these reactions to furnish an easy route to the required cortical analogues, ethynylhexahydroindanol was converted into its acetate (I; R = Ac) and Reichstein's method (*Helv. Chim. Acta*, 1947, **30**, 1616) was adopted. Treatment with *N*-bromoacetamide gave the ωω-dibromo-ketone (VI), which was smoothly debrominated with zinc dust in glacial acetic acid to the ketone (VII). Alternatively, direct addition of aniline to the acetate (I; R = Ac) followed by hydrolysis again gave (VII). This was converted into 1-acetoxy-1-ω-bromoacetylhexahydroindane, and on treatment of this with sodium hydroxide in methanol the bromine atom was replaced by hydroxyl and the ester group was hydrolysed : 1-glycollylhexahydroindan-1-ol (VIII) resulted.



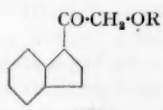
(VI)



(VII)



(VIII)



(IX)

A similar series of reactions on *cis*-1-ethynylhexahydro-8-methylindanol gave the 8-methyl analogue of (VII). Finally for the purposes of biological comparison some related substances were synthesised. The counterpart of (VII) in the decalin series was obtained from *trans*-1-ethynyldecalol. In contrast to the indane compound, 1-acetoxy-1-

ethynyldecalin was easily separated into a crystalline solid and a viscous oil: each was carried separately through the same reactions, to give two 1-acetoxy-1-acetyldecalins, probably isomeric about $C_{(1)}$.

Finally *cis*-hexahydroindane-1-carboxylic acid was converted *via* the diazo-ketone into *cis*-1-ω-acetoxyacetyl- and *cis*-1-glycollylhexahydroindane (IX; R = H and Ac respectively).

Through the courtesy of Dr. A. E. Kellie of the Courtauld Institute of Biochemistry and Dr. R. N. Jones of the National Research Council of Canada, the structurally significant infra-red bands in the annexed Table are recorded. Bands around 1405 cm.$^{-1}$ due to

Substance	Absorption max. (cm.$^{-1}$)	Assignment
1-Acetylhexahydroindane (IX; R = H)	1708 *	Carbonyl
	1353	Acetyl-methyl
(IX; R = Ac)	1753,* 1728, 1705	Carbonyl
	1370	Acetate methyl
(VII)	1732,† 1711	Carbonyl
	1372	Acetate-methyl
	1355	Acetyl-methyl
8-Me homologue of (VII)	1732,† 1711	Carbonyl
	1385	Angular methyl (infl.)
	1372	Acetate-methyl
	1356	Acetyl-methyl
1-Acetoxy-1-ethylhexahydroindane (VIII)	1727 ‡	Carbonyl
	1380	Side-chain methyl
	1367	Acetate-methyl
	3570,† 3430	Hydroxyl
	1710	Carbonyl
	1405	Side-chain methylene
1-Acetoxy-1-acetyldecalin liquid	1732,‡ 1710	Carbonyl
	1372	Acetate-methyl
	1355	Acetyl-methyl
1-Acetoxy-1-acetyldecalin solid	1740,† 1716	Carbonyl
	1370	Acetate-methyl
	1355	Acetyl-methyl

Solvents: * CS_2; † $CHCl_3$; ‡ CCl_4.

unperturbed methylene groups were given by all the compounds. Dr. R. N. Jones reports: "By and large the agreement with true steroids is excellent. Not only do we recognise the same characteristic carbonyl frequencies but also the angular-methyl band at 1380—1385, the acetyl-methyl group at 1350—1355, the acetate-methyl at 1370 and the acetoxymethyl-methylene band at 1410—1415 cm.$^{-1}$."

Experimental

Quantitative hydrogenations were on a micro-scale with PtO_2.

1-Ethynylhexahydroindan-1-ol (I; R = H).—Hexahydroindanone (Mathieson, *J.*, 1953, 3248) (10·6 g.) in dry benzene (200 ml.) was added to a solution from potassium (20 g.) in *tert.*-amyl alcohol (260 ml.). This was added dropwise with stirring during 20 min. to dry ether (500 ml.) through which acetylene had been bubbling for 1 hr. Stirring and passage of acetylene was continued for 7 hr. A saturated solution of ammonium chloride (150 ml.) was then added followed by concentrated hydrochloric acid to acidity to Congo-red. Ether-extraction gave the *acetylene* as a colourless oil (10 g.), b. p. 73°/1 mm., n_D^{18} 1·5042 (Found: C, 80·0; H, 9·7; absorbed 2·0 H_2. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%). The 3:5-*dinitrobenzoate* crystallised from aqueous ethanol in needles, m. p. 114—115° (Found: C, 60·0; H, 4·8; N, 8·1. $C_{18}H_{18}O_6N_2$ requires C, 60·3; H, 5·0; N, 7·8%).

The acetylenic alcohol (8·5 g.) in dry pyridine (25 ml.) was refluxed with acetic anhydride (25 ml.) for 15 hr. Pouring on ice and ether-extraction gave the *acetate* (I; R = Ac) (8 g.), b. p. 80°/3 mm., n_D^{18} 1·4860 (Found: C, 75·8; H, 8·9. $C_{13}H_{18}O_2$ requires C, 75·8; H, 8·7%). This ester absorbed 2 mols. of hydrogen in ethyl acetate at Adams's platinum oxide to give *1-acetoxy-1-ethylhexahydroindane*, b. p. 94—96°/3 mm., n_D^{22} 1·4700 (Found: C, 74·5; H, 10·7. $C_{13}H_{22}O_2$ requires C, 74·3; H, 10·5%).

Rupe Rearrangement of the Alcohol (I; R = H).—(*a*) 1-Ethynylhexahydroindanol (5 g.) was refluxed for 50 min. under nitrogen with 90% formic acid (30 ml.). After neutralisation with sodium hydroxide, ether-extraction gave a colourless oil (2·44 g.) which was fractionated, with the results tabulated.

B. p./1·5 mm.	Yield (mg.)	Micro-hydrogen (H_2, mols.)	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	Reaction with $AgNO_3$	Semi-carbazone	Iodoform test
52—55°	434	2·0	233	3950	Ppt.	−	−
55—65	240	1·5	234	4600	Ppt.	−	−
65—70	414	0·8	237	2600	Faint ppt.	+	−
70	546	0·65	248	2300	No ppt.	+	+

(*b*) 1-Ethynylhexahydroindanol (10·3 g.) with boiling 90% formic acid for 2½ hr. gave a colourless oil (2·3 g.), b. p. 79—89°/8 mm. Based on semicarbazone formed the yield is 16—20%. The *semicarbazone* crystallised in colourless plates from 50% ethanol and after five recrystallisations had m. p. 139—141° (Found : C, 65·2; H, 8·8; N, 19·1. $C_{12}H_{19}ON_3$ requires C, 65·2; H, 8·6; N, 19·0%), $\lambda_{max.}$ 228 mμ (ε 17,380). Decomposition of a sample of semicarbazone, m. p. 128—138° ($\lambda_{max.}$ 230 mμ, ε 15,330) with sulphuric acid gave the *acetylindane* (III), b. p. 91°/10 mm., n_D^{21} 1·5080 (Found : C, 80·9; H, 9·9; absorbed 0·9 H_2. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%). That no rearrangement had occurred during decomposition of the semicarbazone was shown by re-formation of the semicarbazone, m. p. 128—138°. The brick red 2 : 4-*dinitrophenylhydrazone* was unstable on recrystallisation; a crude sample had m. p. 140—142° (Found : N, 16·2. $C_{17}H_{20}O_4N_4$ requires N, 16·3%).

Hydrogenation (palladium in ethanol) of the ketone gave 1-acetylhexahydroindane which after reduction with lithium aluminium hydride in ether gave the alcohol (IV), identified as 3 : 5-dinitrobenzoate (see below).

3-*Ethynyl*-2 : 4 : 5 : 6 : 7 : 8-*hexahydroindene* (II).—Phosphorus oxychloride (6 ml.) in dry pyridine (5 ml.) was added dropwise to the alcohol (I; R = H) (6·6 g.) in pyridine (12 ml.) at such a rate that gentle reflux was maintained. After 1 hr. at 100° the dark mixture was poured on ice. Extraction with light petroleum (b. p. 40—60°) gave the *hydrocarbon* (3·8 g.), b. p. 75°/12 mm., n_D^{25} 1·5205 (Found : C, 88·9; H, 9·7; absorbed 2·6 H_2. $C_{11}H_{14}$ requires C, 90·4; H, 9·7%), $\lambda_{max.}$ 234 mμ (ε 12,790). This material polymerised fairly rapidly at room temperature. It failed to form an adduct with maleic anhydride or benzoquinone in refluxing benzene.

3-*Acetyl*-2 : 4 : 5 : 6 : 7 : 8-*hexahydroindene* (V).—The hydrocarbon (II) (3·2 g.) in benzene (250 ml.) was added to a solution of mercuric chloride (12·9 g.) in water (13 ml.) and aniline (2·3 g.) in benzene (350 ml.). The mixture was stirred at 60° for 18 hr. Hydrochloric acid (36% w/w) (2·43 ml.) was added and the whole was saturated with hydrogen sulphide. After filtration and washing of the precipitate with benzene the combined benzene layers yielded the *ketone* (2·1 g.), b. p. 117—119°/12 mm. A sample purified *via* the semicarbazone had b. p. 101—102°/8 mm., n_D^{20} 1·5110 (Found : C, 80·3; H, 9·7. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%), $\lambda_{max.}$ 253 mμ (ε 8000), $\lambda_{max.}$ (in CS_2) 1670 cm.$^{-1}$. The *semicarbazone* crystallised in colourless needles (from ethanol), m. p. 211—212° (Found : C, 65·6; H, 8·4; N, 19·3. $C_{12}H_{19}ON_3$ requires C, 65·2; H, 8·6; N, 19·0%), $\lambda_{max.}$ 268 mμ (ε 20,000). The 2 : 4-dinitrophenylhydrazone proved to be unstable. Catalytic hydrogenation of this ketone at a palladium–barium sulphate catalyst led to the absorption of 1·84 atoms of hydrogen per mole; the 2 : 4-dinitrophenylhydrazone of the resultant 1-acetylhexahydroindane had m. p. 97—98°, identical with a specimen described below.

cis-1-*Acetylhexahydroindane*.—Cadmium chloride (20 g.) was added to the Grignard reagent from magnesium (4·8 g.) and sufficient methyl bromide to react with all the magnesium. To this dimethylcadmium, *cis*-hexahydroindan-1-carbonyl chloride (18·6 g.) in dry ether (60 ml.) was added dropwise with stirring and the whole was refluxed for 4 hr. After a further 24 hr. at room temperature the mixture was poured on ice, sufficient dilute sulphuric acid being used to dissolve the cadmium salts. Ether-extraction gave an almost colourless oil which was warmed with 10% potassium hydroxide solution for 3 hr., to cleave any ester formed. Ether-extraction of the alkaline residue gave the *acetyl* compound (11·2 g.), b. p. 122°/15 mm., n_D^{20} 1·4808 (Found : C, 79·3; H, 10·9. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in orange-yellow plates, m. p. 97—98° (Found : C, 58·8; H, 6·7; N, 16·1. $C_{17}H_{22}O_4N_4$ requires C, 59·0; H, 6·4; N, 16·2%). The *semicarbazone* crystallised from ethanol in colourless needles, m. p. 187—188° (Found : C, 64·4; H, 9·5; N, 18·5. $C_{12}H_{21}ON_3$ requires C, 64·6; H, 9·4; N, 18·8%).

Hexahydro-1-1′-*hydroxyethylindane*.—1-Acetylhexahydroindane (1·78 g.) in dry ether (50 ml.) was added dropwise to a solution of lithium aluminium hydride (1·8 g.) in dry ether (75 ml.). When gas evolution had ceased water was carefully added to destroy excess of reagent, and the mixture was acidified. Ether-extraction yielded the *alcohol* (1·19 g.), b. p. 70—72°/0·1 mm., n_D^{25} 1·4897 (Found : C, 78·4; H, 12·2. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). The α-*naphthylurethane* crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 106·5—108° (Found : C, 78·3; H, 8·1; N, 4·3. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·1; N, 4·2%). The 3 : 5-*dinitrobenzoate* crystallised in needles, m. p. 89—90·5°, from 90% ethanol (Found : C, 59·7; H, 6·1; N, 7·6. $C_{18}H_{22}O_6N_2$ requires C, 59·7; H, 6·1; N, 7·7%).

1-*Acetylhexahydroindan*-1-*yl Acetate* (VII).—(*a*) Mercuric chloride (18·2 g.) in water (140 ml.) was added to a solution of 1-ethynylhexahydroindan-1-yl acetate (7 g.) and aniline (3·2 g.) in

benzene (700 ml.), and the whole stirred at 60° for 24 hr. Concentrated hydrochloric acid (3 g.) was next added and the mixture was saturated with hydrogen sulphide. After filtration, the aqueous layer was extracted with benzene. The combined organic layers yielded the required *compound* (4 g.), which sublimed at 80°/10 mm. Crystallisation from light petroleum (b. p. 40—60°) gave colourless needles, m. p. 68° (Found: C, 69·7; H, 9·0; OAc, 21·8. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0; OAc, 19·2%).

(*b*) 1-Ethynylhexahydroindanyl acetate (I; R = Ac) (2·8 g.) in *tert.*-butanol (35 ml.) was added to a solution of *N*-bromoacetamide (7 g.) and sodium acetate (7 g.) in water (35 ml.). Acetic acid (35 ml.) was then added dropwise with stirring. After 2 hr. a colourless precipitate resulted. The mixture was cooled to 0°, then filtered, 1-*acetoxy*-1-(ωω-*dibromacetyl*)*hexahydroindane* (VI) resulting (4·1 g.). This crystallised from light petroleum (b. p. 80—100°) in colourless needles, m. p. 92—93° (Found: C, 40·8; H, 4·7. $C_{13}H_{18}O_3Br_2$ requires C, 40·8; H, 4·7%). Bromine analyses were variable. This dibromo-ketone (3 g.) was shaken at 80° for 10 min. with zinc dust (12 g.) and sodium acetate trihydrate (12 g.) in acetic acid (150 ml.). The supernatant liquors were decanted from the residual zinc which was washed with ether. Evaporation of the combined solvents gave a residue (1·3 g.) which crystallised from light petroleum (b. p. 80—100°) at −50° in needles, m. p. 64—65°, identical with a sample synthesised as in (*a*) above.

1-*Glycolloylhexahydroindan*-1-*ol* (VIII).—The above compound (VII) (7·6 g.) was dissolved in glacial acetic acid (200 ml.) at 50° and to the solution was added bromine (6 g.) in acetic acid (100 ml.), followed by a few drops of hydrogen bromide in the same solvent. After 30 minutes' stirring the almost colourless solution was poured into water and the precipitate crystallised from light petroleum (b. p. 60—80°). 1-*Bromoacetylhexahydroindane*-1-*yl acetate* (8·16 g.) was thus obtained in colourless needles, m. p. 118—119° (Found: C, 51·2; H, 6·3; Br, 26·9. $C_{13}H_{19}O_3Br$ requires C, 51·5; H, 6·3; Br, 26·4%).

The bromo-ketone (5 g.) in ether (20 ml.) was added to sodium hydroxide (1·5 g.) in 50% aqueous methanol (400 ml.). After 1 hr. at room temperature under nitrogen, the solution was made faintly acid to litmus with concentrated hydrochloric acid, then evaporated under reduced pressure to one-third of its volume. The residue was saturated with salt and extracted with ether, to give the *diol* (VIII) (1·2 g.), crystallising from light petroleum (b. p. 60—80°) in plates, m. p. 108° (Found: C, 66·7; H, 9·0. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%). This reduced Fehling's solution and gave a silver mirror with ammoniacal silver nitrate.

cis-*Hexahydro*-8-*methylindanone*.—This was synthesised essentially as described by Bachmann and Kushner (*J. Amer. Chem. Soc.*, 1943, **65**, 1963).

cis-1-*Ethynylhexahydro*-8-*methylindanol* was prepared, in the manner described above for 1-ethynylhexahydrindanol, from *cis*-hexahydro-8-methylindanone (7·5 g.). It was obtained as a colourless oil (2·7 g.), b. p. 104°/8 mm. (Found: C, 80·5; H, 10·0; absorbs 2·0 H_2. $C_{12}H_{18}O$ requires C, 80·9; H, 10·1%). Subsequent steps were identical with those described for the corresponding substances lacking the 8-methyl group.

cis-1-*Ethynylhexahydro*-8-*methylindanyl acetate* had b. p. 106°/9 mm. (Found: C, 76·5; H, 8·9. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%).

cis-1-*Acetoxy*-1-(ωω-*dibromoacetyl*)*hexahydro*-8-*methylindane* crystallised from light petroleum (b. p. 60—80°) in pale buff needles, m. p. 141° (Found: C, 42·1; H, 4·9. $C_{14}H_{20}O_3Br_2$ requires C, 42·4; H, 5·1%).

cis-1-*Acetylhexahydro*-8-*methylindan*-1-*yl acetate* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 52—53° (Found: C, 70·3; H, 9·1. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·2%). Under the usual conditions, neither this compound nor (VII) formed a 2:4-dinitrophenylhydrazone or semicarbazone.

trans-1-*Ethynyldecal*-1-*yl Acetate*.—*trans*-1-Ethynyldecal-1-ol (Dimroth, *Ber.*, 1938, **71**, 1333) (17 g.) with acetic anhydride in dry pyridine gave the acetate (18·5 g.), b. p. 96°/2 mm., n_D^{18} 1·4955. Crystallised from light petroleum (b. p. 40—60°; 40 ml.) at 0° an *isomer* (6·5 g.) was obtained which, recrystallised from the same solvent, had m. p. 79—80° (Found: C, 76·6; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%). After removal of all crystalline material the residue, a viscous oil, had b. p. 127°/8 mm., n_D^{20} 1·4960 (10 g.) (Found: C, 76·4; H, 9·2%). These fractions are designated (sol.) and (liquid) respectively. The mixture of the two acetates absorbed four atoms of hydrogen per mole at PtO_2 in ethanol, yielding 1-*acetoxy*-1-*ethyldecalin*, b. p. 135°/15 mm., n_D^{22} 1·5751 (Found: C, 75·0; H, 10·5. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·7%). The undernoted compounds were obtained in the manner described above for the synthesis of the indane derivatives (VI) and (VII).

1-*Acetoxy*-(ωω-*dibromoacetyl*)*decalin* (sol.) crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 93° (Found: C, 43·0; H, 4·9. $C_{14}H_{20}O_3Br_2$ requires C, 42·4; H, 5·1%).

1-*Acetyldecal*-1-*yl acetate* (sol.) was obtained as a viscous colourless oil, b. p. 114°/3 mm., n_D^{18} 1·4862 (Found : C, 70·9; H, 9·2; OAc, 18·1. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·2; OAc, 18·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in light yellow plates, m. p. 179—180° (Found : C, 57·6; H, 6·0; N, 13·3. $C_{20}H_{26}O_6N_4$ requires C, 57·5; H, 6·2; N, 13·4%).

1-Acetoxy-1-(ωω-dibromoacetyl)decalin (liq.) decomposed on attempted purification and the crude material was carried on to the next stage, giving 1-*acetyldecal*-1-*yl acetate* (liq.) as a colourless oil, b. p. 122°/3 mm., n_D^{18} 1·4910 (Found : C, 70·4; H, 9·2; OAc, 18·2. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·2; OAc, 18·1%).

cis-1-*Acetoxyacetylhexahydroindane* (IX; R = Ac).—*cis*-Hexahydroindane-1-carboxylic acid (Mathieson, *J.*, 1953, 325) (1·16 g.) was refluxed with thionyl chloride (3 ml.) in dry benzene (5 ml.). The acid chloride (1·2 g.), b. p. 115—116°/6 mm., in dry ether was added to ethereal diazomethane (from *N*-nitrosomethylurea, 3·5 g., in ether, 50 ml.). After 16 hr. at room temperature removal of ether gave the *diazo-ketone* which crystallised from light petroleum (b. p. 40—60°) in yellow needles, m. p. 70—71° (decomp.) (Found : N, 14·2. $C_{11}H_{16}ON_2$ requires N, 14·6%). The diazo-ketone (1·12 g.) was then warmed with glacial acetic acid (10 ml.) on the water-bath until evolution of nitrogen was complete (20 min.). Evaporation of the acetic acid under reduced pressure gave a residue which slowly solidified. This sublimed at 80°/0·05 mm. (1·11 g.). Crystallisation from light petroleum (b. p. 60—80°) gave needles, m. p. 60—62° (Knowles, Kuck, and Elderfield, *J. Org. Chem.*, 1942, **7**, 377, give m. p. 59—61°). The *semicarbazone* crystallised from ethanol in colourless needles, m. p. 171—172° (Found : C, 59·7; H, 8·3; N, 14·7. $C_{14}H_{23}O_3N_3$ requires C, 59·8; H, 8·2; N, 15·0%).

cis-1-*Hydroxyacetylhexahydroindane* (IX; R = H).—The diazo-ketone (from hexahydroindane-1-carboxylic acid, 5 g.) in dioxan (25 ml.) was warmed on the steam-bath for 30 min. with N-sulphuric acid (40 ml.). The mixture was diluted with water (200 ml.) and extracted with ether, to yield a light yellow oil, b. p. 90—95°/0·05 mm., which slowly solidified (2·65 g.). Crystallisation from light petroleum (b. p. 60—80°) gave the *ketol* as colourless needles, m. p. 99° (Found : C, 72·4; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·6; H, 9·9%).

Microanalyses were carried out by Mr. G. H. Crouch of this College. One of us (D. W. M.) thanks Imperial Chemical Industries Limited for the award of an I.C.I. Fellowship. Another (L. E. C.) is indebted to the D.S.I.R. for a maintenance grant.

School of Pharmacy, University of London,
17 Bloomsbury Square, London, W.C.1. [*Received, March 11th*, 1954.]

The Gum of Acacia pycnantha.

By E. L. Hirst and A. S. Perlin.

[Reprint Order No. 5235.]

The gum exuded by *Acacia pycnantha* has been compared with other types of *Acacia* gum. It gives on hydrolysis D-galactose (65%), L-arabinose (27%), L-rhamnose (1—2%), and D-glucuronic acid (5%). Partial hydrolysis affords the aldobiuronic acid 6-*O*-β-D-glucuronosyl-D-galactose and a disaccharide, probably 3-*O*-β-D-galactopyranosyl-D-galactose. Evidence has been obtained that the molecular structure is complex and probably highly branched and it appears that gums from various species of *Acacia* must differ markedly in structural details.

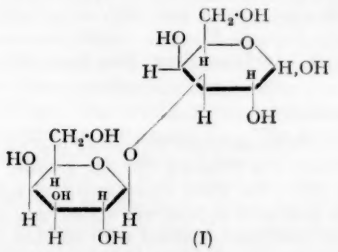
Gums have been isolated from many species of *Acacia* and, of these, gum arabic has been studied most extensively (O'Sullivan, *J.*, 1884, **41**; Butler and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 1519; Challinor, Haworth, and Hirst, *J.*, 1931, 258; Smith, *J.*, 1939, 744, 1724; Jackson and Smith, *J.*, 1940, 74, 79; Dillon, O'Ceallachain, and O'Colla, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 331). In this gum L-rhamnose (1 mol.), L-arabinose (3 mols.), D-galactose (3 mols.), and D-glucuronic acid (1 mol.) are glycosidically linked in a highly branched, complex pattern. The gum of *Acacia mollissima* Willd. (black-wattle gum) is of similar type but differs in containing a smaller proportion (approximately half) of glucuronic acid. Like gum arabic it gives rise on partial hydrolysis to the aldobiuronic acid 6-glucuronosido-galactose (Stephen, *J.*, 1951, 646). The gum of *Acacia pycnantha*, which is the

subject of the present paper, does not appear to have been examined and it was of interest therefore to determine what relation it bears to the other gums of the *Acacia* family.

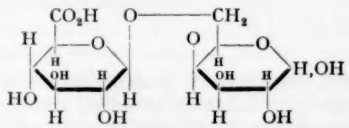
The gum was made available through the kindness of Mr. J. E. Cummins of the Australian Scientific Liaison Office, London, and Mr. B. H. Bednall, Conservator of Forests, Adelaide. It was in the form of nodules exuded by *A. pycnantha* growing in South Australia. Most of the crude gum was readily soluble in water but approximately 3% formed a dense gel. The soluble portion was isolated by precipitation with alcohol as colourless, acidic, slightly reducing powder. Hydrolysis and examination of the products on the paper chromatogram indicated the presence of L-rhamnose (1—2%), L-arabinose (27%), and D-galactose (65%). The uronic acid residues (D-glucuronic acid) amounted to approximately 5% of the total. It is possible that the rhamnose is present in an adherent impurity and is not a main structural feature of *A. pycnantha* gum. The insoluble gel was not hydrolysed completely by acid, but the mixture of sugars liberated had essentially the same composition as for the soluble gum, the uronide carbon dioxide figure being somewhat higher and the nitrogen content considerably higher. The gel was evidently a mixture and was not examined further.

The arabinose residues were removed by hydrolysis under mild conditions. The rhamnose residues were less labile but were liberated more rapidly than galactose, permitting the use of graded hydrolysis to effect a partial separation of rhamnose and arabinose from the greatly predominating galactose. The mixture of free sugars was then separated by partition chromatography on a cellulose column. This gave L-rhamnose, identified as the crystalline hydrate, and larger quantities of L-arabinose and D-galactose, identified as characteristic hydrazones. After removal of the sugars the column was washed with water, giving a mixture of oligosaccharides, which were partially separated on a charcoal–Celite column (Whistler and Durso, *J. Amer. Chem. Soc.*, 1951, **13**, 4189; Peat and Whelan, personal communication). Development of the charcoal column with 7·5% alcohol afforded a fraction from which a crystalline disaccharide was isolated (m. p. 159—160°, $[\alpha]_D$ +62·1° in H_2O) which on hydrolysis yielded only galactose. Evidence obtained by oxidation by lead tetra-acetate (Perlin, forthcoming publication) indicated that this was 3-*O*-β-galactopyranosyl-D-galactose (I). This disaccharide was isolated by Smith (*loc. cit.*) after partial hydrolysis of gum arabic.

Prolonged hydrolysis of the gum followed by neutralisation with barium carbonate and removal of the free sugars afforded a mixture of barium salts. On the paper chromatogram the main component appeared as a slow-moving spot, but there were present some glucuronic acid (as glucurone) and traces of galactose and arabinose. The slow-moving component, obtained as a syrup by elution from the chromatogram, had equivalent weight 347, and $[\alpha]_D$ +16° in water. On further hydrolysis this gave galactose and glucurone. Methano-



(I)



(II)

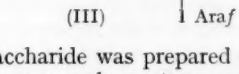
lysis, followed by reduction of the ester with sodium borohydride (Wolfrom and Anno, *J. Amer. Chem. Soc.*, 1952, **74**, 5583) and hydrolysis of the resulting glycosides, gave a mixture of galactose and glucose. These results indicated that the main component of the acidic hydrolysis product was an aldobiuronic acid composed of galactose and glucuronic acid.

By methylation a fully methylated aldobiuronic acid was prepared and this on hydrolysis yielded 2 : 3 : 4-tri-*O*-methyl-D-galactose, identified as the crystalline anilide, and 2 : 3 : 4-

tri-*O*-methyl-D-glucuronic acid, identified as the amide and by conversion into the methyl ester of 2 : 3 : 4-tri-*O*-methyl-D-saccharolactone. Reduction of this methyl ester with sodium borohydride (Wolfrom and Anno, *loc. cit.*) gave only 2 : 3 : 4-tri-*O*-methylglucose, indicating the absence of galacturonic acid. In addition to these two components of the aldobiuronic acid a small quantity of another methylated sugar (R_G, 0·81; OMe, 35%) was found in the products of hydrolysis. The principal aldobiuronic acid is, therefore, 6-β-D-glucuronosyl-D-galactose (II), but in view of the presence of the unidentified sugar the possibility remains that a small proportion of the glucuronic acid residues in the polysaccharide may be linked in some other way.

Periodate oxidation of the gum resulted in consumption of 0·86 mole of periodate per residue with the formation of 0·32 mole of formic acid per residue. Many of the sugar residues in the gum were not attacked by periodate and it follows that the polysaccharide may be highly branched or may contain a proportion of 1 : 3-glycosidic linkages, or both. Since the periodate-oxidised polysaccharide yielded on hydrolysis galactose accompanied by only traces of arabinose it appears that the arabinose residues in the polysaccharide are more open to attack. Since over 90% of the gum is composed of D-galactose and L-arabinose residues in the proportion 2 : 1 one possible type of structural unit would therefore be (III), but it is already clear, as the result of preliminary methylation studies, that the structure must in fact be much more complex.

(III)



The fully methylated polysaccharide was prepared and a preliminary examination of the products of hydrolysis on the paper chromatogram indicated the presence of at least six methylated sugars. From their positions on the paper these appeared to be (in order) 2 : 3 : 5-tri-*O*-methylarabinose (faint), 2 : 3 : 4 : 6-tetra-*O*-methylgalactose (moderate), an unknown sugar (trace), 2 : 3 : 4-tri-*O*-methylgalactose (moderate), a di-*O*-methylgalactose (strong), an unknown sugar (faint), and a methylated uronic acid (trace). This mixture will be further investigated but these observations are sufficient to support the indication given by periodate oxidation that the polysaccharide has a highly branched structure.

The polysaccharide of *A. pycnantha* therefore resembles gum arabic and black-wattle gum in that it contains the same constituent sugars and yields the same aldobiuronic acid. Nevertheless, the proportions of the sugar residues present in the various *Acacia* gums are markedly different (see Table), and the detailed structures must therefore differ considerably.

	Rhamnose	Arabinose	Galactose	Glucuronic	Equiv. wt.
Arabic [a]	14	34	42	15	1000
Black wattle [b]	8	46	38	8	1880
A. pycnantha	2	27	65	4	3700

[a] Pigman and Goepp, " Chemistry of the Carbohydrates," Academic Press, New York, 1948, p. 633.
[b] Stephen, *loc. cit.*

Experimental

The gum was composed of amber to dark brown nodules admixed with small particles of bark. The nodules were taken up in water, and the solution was strained through muslin, and then centrifuged, depositing a small quantity of dense gel. The clear straw-coloured supernatant liquor was acidified (pH 2) with dilute hydrochloric acid, and alcohol was added to a concentration of 80%. The precipitate was removed on the centrifuge, washed with alcohol and ether, and dried *in vacuo*. Addition of alcohol to the gel caused solidification and the solid was washed with alcohol and ether and dried *in vacuo*. In a typical preparation, 100 g. of crude gum yielded 78·2 g. of the water-soluble fraction and 2·85 g. of gel.

Preliminary Examination.—The main fraction was a white powder, $[\alpha]_D$ −8·1° (*c*, 2·7 in H_2O) [ash, 0·33%; N, 0·5%; reducing power, 10 g. required 4·4 c.c. of 0·1N-iodine; CO_2H (by titration), 0·8%; uronide CO_2 liberated by boiling 12 or 19% hydrochloric acid, 1·0—1·2% (corrected for non-uronide CO_2)]. When the substance was hydrolysed at 2% concentration with 0·5N-sulphuric acid in a sealed tube at 100° the specific rotation ($[\alpha]_D$) rose to the constant value +83°. Examination of the neutralised hydrolysate on the paper chromatogram indicated the presence

of rhamnose, galactose, and arabinose. Quantitative estimation of the sugars separated on the chromatogram by periodate oxidation (Hirst and Jones, *J.*, 1949, 1659) and by the Somogyi reagent (Somogyi, *J. Biol. Chem.*, 1945, **160**, 61) gave rhamnose 1—2%, arabinose 27%, and galactose 65%. The rotation of an aqueous solution of L-arabinose and D-galactose mixed in these proportions is $[\alpha]_D$ +87°. These figures together with 5% of uronic anhydride indicate the approximate composition of the polysaccharide. In another experiment a single nodule of the gum, purified as described above, had the same composition as that of the large-scale preparation, indicating the gum to be essentially homogeneous.

The gel (see above), when dried, gave a coarse grey powder [N, 1·3%; uronide CO_2, 1·7% (corr.)]. Under conditions of hydrolysis as for the soluble gum it did not all dissolve {$[\alpha]_D$ (final) +68°}. On the paper chromatogram of the products only a trace of rhamnose was present but arabinose and galactose were present in the molar ratio 1 : 2·4. The gel was not further examined.

Qualitative experiments in which the gum was boiled (*a*) in aqueous solution and (*b*) with 0·05N-sulphuric acid, indicated that much of the arabinose was liberated rapidly and rhamnose somewhat more slowly, whilst the galactose residues were more resistant to hydrolysis.

Graded Hydrolysis.—The gum (30 g.) in 0·1N-sulphuric acid (1 l.) was heated for 8 hr. at 95°. The solution was then concentrated at 30—35° to 150 c.c. and poured into alcohol (1 l.), giving a precipitate which was separated and dried (12·9 g.) (This precipitate was found on hydrolysis to contain galactose and uronic acid residues.) The supernatant liquor was neutralised with barium carbonate and concentrated to a syrup of which 9 g. were placed on a cellulose column and eluted with *iso*propyl alcohol–water (9 : 1) (Hough, Jones, and Wadman, *J.*, 1949, 2511). The eluted fractions were examined on the paper chromatogram. By combination of appropriate fractions and removal of the solvent the following were obtained: fraction 1, α-L-rhamnose hydrate (120 mg.), $[\alpha]_D$ +9° (*c*, 1·35 in H_2O, final), m. p. 91°, not depressed by admixture with authentic α-L-rhamnose hydrate, m. p. 92°; the *X*-ray powder diagram was identical with that of α-L-rhamnose hydrate. Fraction 2, L-arabinose (2·5 g.), $[\alpha]_D$ +100° (*c*, 1·1 in H_2O, equil.) [benzoylhydrazone, m. p. and mixed m. p. 185—187° (decomp.)]. Fraction 3, D-galactose (2·4 g.), $[\alpha]_D$ +81·5° (*c*, 1·0 in H_2O, final); recrystallised from aqueous methanol this gave α-D-galactose hydrate, m. p. 119° (methylphenylhydrazone, m. p. and mixed m. p. 182°).

The cellulose column was washed with water, and the eluate was concentrated to a syrup (3·2 g.), which showed several components on a paper chromatogram, the fastest of which corresponded to di- and tri-saccharides. The syrup was transferred to a charcoal–Celite (1 : 1) column (Whistler and Durso, *loc. cit.*) which was developed with 7·5% alcohol, 100-c.c. fractions being collected and examined chromatographically. The early fractions contained at least three components; fractions 6—10 appeared to consist mainly of one component, which appeared to be a disaccharide. Fractions 6—10 were combined and concentrated to a syrup (0·45 g.) a portion of which, on hydrolysis, gave on a paper chromatogram galactose (strong) and arabinose (weak). This syrup was then boiled under reflux with 85% methanol. After several weeks in the cold the extract deposited crystals (0·11 g.), m. p. 159—160·5°, $[\alpha]_D$ +62° (equil.; *c*, 0·58 in H_2O), reducing equivalent 366 (a disaccharide, containing two hexose residues, requires 342; for a monohydrate, 360). After hydrolysis with 0·5N-sulphuric acid $[\alpha]_D$ was +76·5° and the hydrolysate, examined on a paper chromatogram, contained only galactose.

Isolation of an Aldobiuronic Acid.—The gum (40 g.) in N-sulphuric acid (800 c.c.) was heated at 95° for 7·5 hr. The solution was neutralised ($BaCO_3$), concentrated to 150 c.c., and added slowly with stirring to ethanol (1 l.). The precipitate was collected on the centrifuge, extracted 4 times with boiling methanol, washed with ether, and dried *in vacuo* (1·57 g.; Ba, 15·5%; OMe, 1·4%). On a paper chromatogram (developed with ethyl acetate–acetic acid–formic acid–water, 9 : 1·5 : 0·5 : 2) (Jones and Wise, *J.*, 1951, 2750), the crude barium salt gave a main component close to the origin, traces of two slightly faster moving substances, and traces of arabinose, galactose, and uronic acid; the last two travelled at similar rates but were differentiated by development with *p*-anisidine hydrochloride (Hough, Jones, and Wadman, *J.*, 1950, 1702) and examination in ultra-violet light. Galactose gave a yellow, and the uronic acid a deep red, fluorescence. The main component, isolated by chromatography on sheets of Whatman 3MM paper, had an equivalent 347 (an aldobiuronic acid requires 356) and $[\alpha]_D$ +16° (*c*, 0·2 in H_2O). On hydrolysis in a sealed tube at 100° for 3·5 hr. with 3N-sulphuric acid it yielded galactose and glucuronic acid, the latter appearing on the chromatogram as glucurone when the partly neutralised hydrolysate was examined. A portion (200 mg.) of the aldobiuronic acid was boiled with 8% methanolic hydrogen chloride for 7 hr.; the solution was neutralised and the alcohol removed. A solution of the product in water (2 c.c.) was added dropwise with stirring during

5 min. to a solution of sodium borohydride (0·1 g.) in water (1·5 c.c.) (Wolfrom and Anno, *loc. cit.*). After 15 min., the excess of borohydride was destroyed with dilute acetic acid, the solution was de-ionised with resins, and the glycosides were hydrolysed with sulphuric acid. On a paper chromatogram the hydrolysate was then found to contain galactose and glucose. Treatment of the mixture of sugars with a sample of glucose oxidase (notatin), known to be specific for glucose, removed the material which had previously corresponded to glucose on the chromatogram and left only galactose.

Structure of the Methylated Aldobiuronic Acid.—The crude barium salt (3·1 g.) prepared by hydrolysis of the gum (74 g.) under the conditions previously described was methylated twice with methyl sulphate (20 c.c.) and sodium hydroxide (40 c.c.; 40%). The alkaline solution was extracted with chloroform to remove non-acidic methylated sugars, and after acidification (sulphuric acid) again extracted with chloroform. The second extract was concentrated to a syrup which was methylated twice with methyl iodide and silver oxide giving a syrup (1·2 g.; OMe, 45%). Further treatment with methyl iodide and silver oxide failed to raise the methoxyl value. By repeatedly extracting the syrup with boiling light petroleum (b. p. 40—60°) a clear pale yellow oil (0·93 g.; n_D^{20} 1·4680; OMe, 49·5%) was removed leaving some dark insoluble wax. The oil, purified by distillation, had b. p. (bath-temp.) 160—190°/0·02 mm., n_D^{17} 1·4640, $[\alpha]_D$ −5° (*c*, 3·0 in H_2O) (OMe, 50·6. Calc. for a fully methylated aldobiuronic acid, 53·0%).

This methyl hepta-*O*-methylaldobiuronate (0·3 g.) was heated at 100° for 7 hr. The solution was neutralised with silver carbonate, treated with hydrogen sulphide, and neutralised with barium carbonate. The filtrate was concentrated to a syrup from which traces of water were removed by repeated addition and distillation of alcohol. Exhaustive extraction of the syrup with boiling ether (A) left a barium salt {0·16 g., $[\alpha]_D$ +66° (*c*, 1·0 in H_2O)}. This was boiled with 3% methanolic hydrogen chloride, and the product with methanolic ammonia gave the amide of methyl 2 : 3 : 4-tri-*O*-methyl-α-D-glucuronide, m. p. 184—185°, after recrystallisation from acetone–ether. The amide and the material in the mother-liquors were transformed into the corresponding methyl ester by reaction with 3% methanolic hydrogen chloride. The ester was reduced with sodium borohydride as described previously. After hydrolysis the product gave only one spot on a paper chromatogram, its position being identical with that of 2 : 3 : 4-tri-*O*-methylglucose and well separated from that of 2 : 3 : 4-tri-*O*-methylgalactose. Another sample (0·24 g.) of the barium salt of the methylated uronic acid prepared by hydrolysis of the fully methylated aldobiuronic acid (0·4 g.) was oxidised with bromine. The product was esterified (3% methanolic hydrogen chloride) and distilled; it had b. p. (bath-temp.) 134—145°/0·1 mm., n_D^{18} 1·4530, and crystallised after 6 weeks at 0°; recrystallisation from ether gave the methyl ester, m. p. 106—107°, of 2 : 3 : 4-tri-*O*-methyl-D-saccharolactone (Found: OMe, 49·5. Calc. for $C_{10}H_{16}O_7$: OMe, 50·0%).

The ether extract (A, above) was concentrated to a syrup (0·15 g. from 0·4 g. of methylated aldobiuronic acid), $[\alpha]_D$ +63·5° (*c*, 0·77 in H_2O) (OMe, 36·1%). On a chromatogram it gave a strong spot with R_G that of 2 : 3 : 4-tri-*O*-methylgalactose, and a faint spot (R_G 0·81) which travelled more rapidly. These components were separated by chromatography on sheets of 3MM paper. The major component {OMe, 39·2%; $[\alpha]_D$ +80° (*c*, 1·0 in H_2O)} on treatment with aniline in boiling alcohol gave 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-galactopyranosylamine, m. p. and mixed m. p. 164—165° after recrystallisation from alcohol–ether. The minor component {MeO, 35·0%; $[\alpha]_D$ +4·5° (*c*, 0·5 in H_2O)} was oxidised by sodium metaperiodate with formation of formaldehyde as indicated by the Rimini ferricyanide–phenylhydrazine test (*Bull. Soc. chim.*, 1898, **20**, 896).

Oxidation of the Gum with Sodium Metaperiodate.—The gum (100 mg.) was dissolved in water (58 c.c.) containing sodium metaperiodate (0·4 g.), and the solution was kept at 16° in the dark. Portions of 5 c.c. were withdrawn at intervals and titrated with 0·005N-sodium hydroxide after destruction of excess of periodate with ethylene glycol: 3·21 c.c. (24 hr.), 3·46 c.c. (72 hr.), 3·65 c.c. (120 hr.), the last corresponding to *ca.* 0·32 mole of formic acid per residue (consumption of periodate at this stage was 0·86 mole per residue). Potassium chloride was added to the remaining solution of oxidised gum, and the salts were removed by dialysis. The product, after hydrolysis with boiling 0·5N-sulphuric acid, gave on a paper chromatogram indications of galactose (strong) and arabinose (trace).

Methylation of the Gum.—The gum (24 g.) in water (300 c.c.) was methylated in the usual way by sodium hydroxide (310 c.c.; 40%) and methyl sulphate (230 c.c.) under nitrogen. The methylation was repeated twice and the product was then methylated five times with silver oxide and methyl iodide. The product was fractionally precipitated by light petroleum (b. p. 60—80°) from its solution in chloroform. Almost the whole of it came down as material having

$[\alpha]_D$ −48° in $CHCl_3$ (*c*, 1·0) and OMe, 40·5%. No change was effected by further methylation and the material could not be separated by fractional dissolution into fractions differing appreciably in proportions. This methylated polysaccharide (50 mg.) was dissolved in dry methanol (5 c.c.), dry IR-120 resin (150 mg.) was added, and the mixture heated in a sealed tube for 18 hr. at 100°. The product was heated with 0·6N-hydrochloric acid (5 c.c.) in a sealed tube at 100° for 8 hr. The product, isolated in the usual way, was examined on a paper chromatogram, at least six components being observed. By comparison with authentic materials these components corresponded, in decreasing order of rate of movement, to 2 : 3 : 5-tri-*O*-methylarabinose (faint), 2 : 3 : 4 : 6-tetra-*O*-methylgalactose (moderate), an unidentified substance (trace), 2 : 3 : 4-tri-*O*-methylgalactose (moderate), a di-*O*-methylgalactose (strong), an unidentified substance (faint), and a methylated uronic acid (faint).

We thank Mr. J. E. Cummins and Mr. B. H. Bednall for providing the sample of gum, and the National Research Council of Canada for a grant which enabled one of us (A. P.) to take part in this work.

CHEMISTRY DEPARTMENT, THE UNIVERSITY OF EDINBURGH.
[Present address (A. S. P.): NATIONAL RESEARCH COUNCIL, OTTAWA, CANADA.]

[*Received, March 24th,* 1954.]

The Synthesis of Progesterone and Related Compounds.

By A. F. DAGLISH, J. GREEN, and V. D. POOLE.

[Reprint Order No. 5259.]

Ergosterol has been converted into pregnane-3 : 20-dione, progesterone, and 3α-acetoxypregnan-20-one.

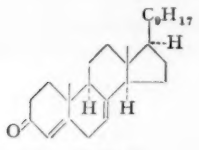
PREGNANE-3 : 20-DIONE, progesterone, and 3α-acetoxypregnan-20-one are useful intermediates in the synthesis of cortisone from readily available steroids and the object of the work described here is to provide a convenient route to these compounds from ergosterol. Preliminary announcements on this subject from the Upjohn Company (*Chem. Eng. News*, 1953, **31**, 3977), Johnson, Newbold, and Spring (*Chem. and Ind.*, 1953, 1230), and ourselves (*ibid.*, p. 1207) have already appeared.

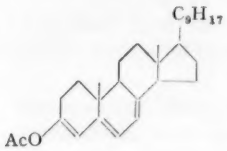
Ergosterone (ergosta-4 : 7 : 22-trien-3-one) (I) was prepared by the Oppenauer oxidation of ergosterol with aluminium *iso*propoxide, *cyclo*hexanone, and benzene or toluene. The use of acetone as hydrogen acceptor gave products which contained unchanged ergosterol. When *iso*butyl methyl ketone and aluminium *iso*propoxide were used in the *absence* of the conventional inert solvent, good yields of ergosterone were obtained.

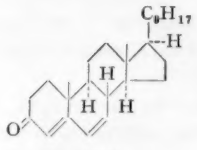
The direct isomerisation of ergosterone to *iso*ergosterone (ergosta-4 : 6 : 22-trien-3-one) (III) in 60% yield by treatment with a chloroform solution of hydrogen chloride has been carried out by Barton, Cox, and Holness (*J.*, 1949, 1771), but this yield is only obtained when the ergosterone has been carefully purified. In order to avoid this wasteful procedure, the crude product from the Oppenauer oxidation was acetylated directly, giving the enol acetate of ergosterone (II) (cf. Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869), which in boiling aqueous-methanolic sulphuric acid afforded *iso*ergosterone in 66% overall yield from ergosterol. Other methods previously described for this conversion (Heilbron *et al.*, *loc. cit.*; Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, 1951, **16**, 1453) were found to give only low yields of highly coloured material. The hydrolysis proceeds through an intermediate compound believed from its analysis and ultra-violet absorption spectrum to be 3-methoxyergosta-3 : 5 : 7 : 22-tetraene. It has $\lambda_{max.}$ at 320 mμ (log ε 4·30), corresponding to a conjugated heteroannular triene, exhibiting the typical bathochromic shift due to methoxyl substitution (cf. Dorfman, *Chem. Reviews*, 1953, **53**, 47). It is easily isolated as it is precipitated from the reaction mixture during the early stages of the hydrolysis.

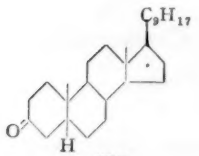
Hydrogenation of a dry ethanolic solution of *iso*ergosterone, in the presence of 10% palladised charcoal and relatively high concentrations of potassium hydroxide, ceased after the uptake of two mols. of hydrogen, yielding 5β-ergost-22-en-3-one (IV). Other

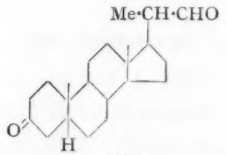
catalyst carriers such as calcium carbonate and barium sulphate were also successful. When a less active palladium catalyst (1% on charcoal) was used with a lower concentration of alkali, and when the hydrogenation was stopped after the uptake of one mol. of hydrogen, ergosta-4 : 22-dien-3-one (VI) (Barton *et al.*, *loc. cit.*) was isolated in good yield. However, this dienone was prepared more conveniently and in excellent yield by treating *iso*-ergosterone in liquid ammonia with lithium or sodium followed by ethanol, according to the general method of Wilds and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 5360). This appears to be the first time that this reagent has been used for the selective reduction of a steroidal conjugated heteroannular dienone.

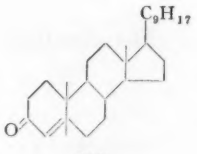

(I)

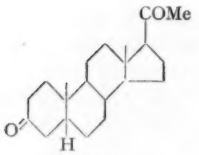

(II)

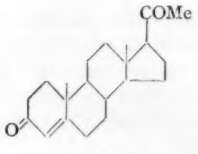

(III)

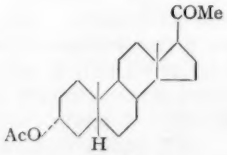

(IV)


(V)


(VI)


(VII)


(VIII)


(IX)

Treatment of a chloroform solution of 5β-ergost-22-en-3-one at −70° with one mol. of ozone gave 3-oxobisnorcholan-22-al (V) in 92% yield. Ozonisation in other solvents was unsatisfactory. When two or more mols. of ozone were used, or when ozonisation was carried out at higher temperatures, the products contained large amounts of 3-oxobisnorcholanic acid. This acid was best obtained by permanganate oxidation of the ozonisation product. The cyclic ketal prepared from 5β-ergost-22-en-3-one and ethylene glycol was ozonised at 0° and gave a mixture from which, on esterification with diazomethane, methyl 3-ethylenedioxybisnorcholanate was isolated. The side chain of this compound could not be degraded further with phenylmagnesium bromide in the usual manner without hydrolysis of the ketal grouping. The only product isolated was 3 : 22 : 22-triphenylbisnorchola-3 : 20(22)-diene.

Treatment of a chloroform solution of ergosta-4 : 22-dien-3-one at −70° with one mol. of ozone gave 3-oxobisnorchol-3-en-22-al, which has been previously prepared from stigmasterol and converted into progesterone by Heyl and Herr (*loc. cit.*; *ibid.*, 1952, **74**, 3627).

3-Oxobisnorcholan-22-al was degraded by way of its enol acetate, prepared by the method of Bergman and Stevens (*J. Org. Chem.*, 1948, **13**, 10). The enol acetate was ozonised, without isolation, giving pregnane-3 : 20-dione (VII). Alternatively, degradation proceeded by way of the 22-piperidino-derivative (cf. Heyl and Herr, *loc. cit.*). This enamine, because of its instability, was difficult to obtain pure, and generally the crude condensation product was ozonised directly, to give the dione.

Hydrogenation of 5β-ergost-22-en-3-one in ethanol, containing potassium hydroxide, with Raney nickel gave 5β-ergost-22-en-3α-ol in 90% yield. (Barton *et al.*, *loc. cit.*, reduced this ketone with sodium and *n*-propanol.) The reduction was also carried out in high

yield with lithium in liquid ammonia, followed by addition of ethanol. 5β-Ergost-22-en-3α-ol was also obtained in good yield by the Raney nickel reduction of either ergost-4 : 22-dien-3-one or *iso*ergosterone, uptake of hydrogen ceasing at 2 and 3 mols. respectively. Acetic anhydride gave the 3α-acetate in 93% yield.

Treatment of a chloroform solution of 3α-acetoxy-5β-ergost-22-ene at −70° with one mol. of ozone gave over 90% of 3α-acetoxybisnorcholan-22-al. When larger amounts of ozone were used at higher temperatures, the main product isolated was the 3α-acetoxy-acid, also obtained in high yield by chromic acid oxidation of the total crude ozonisation product.

3α-Acetoxybisnorcholan-22-al was converted into its enol acetate, which, without isolation, was ozonised in chloroform, giving 3α-acetoxypregnan-20-one (IX). Alternatively, the 22-aldehyde gave a crystalline piperidino-derivative in good yield, which, on ozonolysis, also afforded 3α-acetoxypregnan-20-one.

Pregnane-3 : 20-dione, on bromination in methylene chloride–*tert.*-butanol, gave 4-bromopregnane-3 : 20-dione which, on dehydrobromination (cf. McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5813), gave progesterone (VIII).

Experimental

Optical rotations were determined on 0·5—1% solutions in $CHCl_3$ at 15—20°. Ultraviolet absorption measurements were made in ethanolic solution with a Hilger " Uvispek " instrument. Alumina for chromatography was Spence, Type " O."

3-*Acetoxyergosta*-3 : 5 : 7 : 22-*tetraene* (*Ergosterone Enol Acetate*) (II).—(*a*) A mixture of ergosterol (50 g.), *cyclo*hexanone (300 ml.), and benzene (500 ml.) was distilled until moisture had been removed azeotropically. Aluminium *iso*propoxide (40 g.) in dry benzene (250 ml.) was added, and the mixture refluxed for 6 hr. Rochelle salt (50 g.), dissolved in a minimum of water, was then added and the volatile solvents were removed by steam-distillation. While still warm, the residue was extracted with benzene, and the extract washed with water, dried, and evaporated, the last traces of volatile material being removed on a steam-bath under reduced pressure. The crude product, which was a yellow solid, was refluxed with acetic anhydride (50 ml.) and pyridine (50 ml.) for 3 hr. After cooling, the product crystallised from the reaction mixture, which was filtered. Crystallisation from ethyl acetate gave 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene (41 g., 74%) as plates, m. p. 146—149°, $[\alpha]_D$ −143°, $\lambda_{max.}$ 315 mμ (log ε 4·36). Heilbron *et al.* (*loc. cit.*) give m. p. 146°, $[\alpha]_D$ −143·5°, $\lambda_{max.}$ 316·5 mμ (log ε 4·33).

(*b*) Repetition of (*a*) with toluene (1200 ml.) in place of benzene and refluxing for 20—30 min. gave the same yield of 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene.

(*c*) Aluminium *iso*propoxide (15 g.) was refluxed in a dry solution of ergosterol (15 g.) in *iso*butyl methyl ketone (600 ml.) for 2 hr. When cool, the product was washed with dilute sulphuric acid, followed by water until neutral. The solvent was removed and the residue acetylated, affording 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene (11·5 g., 70%) as plates, m. p. 144—147°.

Ergosta-4 : 6 : 22-*triene*-3-one (iso*Ergosterone*) (III).—A suspension of 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene (100 g.) in methanol (5000 ml.), sulphuric acid (150 ml.), and water (125 ml.) was heated under reflux. The enol acetate dissolved rapidly, and during the reaction a white flocculent precipitate appeared, which slowly redissolved. Refluxing was continued for 1 hr. after the final clearing of the solution, the total reaction period being approx. 3 hr. The solution was cooled to room temperature and an equal volume of water added. The precipitated solid was collected and dissolved in ether, and the extract washed with water until free from acid. Evaporation left crude ergosta-4 : 6 : 22-trien-3-one which crystallised from methanol as faintly yellow needles (78 g., 87%), m. p. 106·5—108·5°, $[\alpha]_D$ −40°, $\lambda_{max.}$ 283 mμ (log ε 4·44). Heilbron *et al.* (*loc. cit.*) give m. p. 108°, $[\alpha]_D$ −30°, $\lambda_{max.}$ 280 mμ (log ε 4·52).

3-*Methoxyergosta*-3 : 5 : 7 : 22-*tetraene*.—The above hydrolysis was repeated and, after 1 hour's refluxing, a portion of the insoluble intermediate was filtered off, washed with hot methanol, and crystallised twice from ethyl acetate, yielding 3-*methoxyergosta*-3 : 5 : 7 : 22-*tetraene* as needles, m. p. 137—140°, $\lambda_{max.}$ 320 mμ (log ε 4·30) (Found: C, 85·3; H, 11·0. $C_{29}H_{44}O$ requires C, 85·2; H, 10·9%). This substance is unstable, especially in chloroform solution, but an ether solution gave $[\alpha]_D$ −75°.

5β-*Ergost*-22-*en*-3-*one* (IV).—A solution of potassium hydroxide (50 g.) in pure, dry ethanol (5 l., distilled over Raney nickel) containing palladium catalyst (10% on charcoal; 20 g.) was

shaken in an atmosphere of hydrogen until the catalyst was saturated. *iso*Ergosterone (100 g.) was added and hydrogenation continued until there was no further uptake of hydrogen (2·0 mols. of hydrogen were absorbed in 2 hr.). After filtration, the solution was made just acid by addition of acetic acid, and the solvent removed under reduced pressure. The product from ether was crystallised from methanol, yielding 5β-ergost-22-en-3-one (81 g., 80%) as plates, m. p. 108—110°. After several recrystallisations from methanol, a sample for analysis had m. p. 114—115°, $[\alpha]_D$ −6° (Found: C, 83·9; H, 11·5. Calc. for $C_{28}H_{46}O$: C, 84·4; H, 11·6%). Barton *et al.* (*loc. cit.*) give m. p. 110·5°, $[\alpha]_D$ −2°.

Ergosta-4 : 22-dien-3-one (VI).—(*a*) A solution of potassium hydroxide (0·1 g.) in dry ethanol (250 ml.), containing palladium catalyst (1%, on charcoal; 1·25 g.), was shaken in an atmosphere of hydrogen until the catalyst was saturated. *iso*Ergosterone (5 g.) was added and reduction continued until 1 mol. of hydrogen had been absorbed, then the reaction was stopped. The product was isolated in the usual manner, affording ergosta-4 : 22-diene-3-one (3·0 g., 60%), m. p. 127—128°, $[\alpha]_D$ +42°, $\lambda_{max.}$ 242 mμ (log ε 4·21). Barton *et al.* (*loc. cit.*) give m. p. 127·5—128·5°, $[\alpha]_D$ +44°, $\lambda_{max.}$ 242 mμ (log ε 4·26).

(*b*) *iso*Ergosterone (1·0 g.) was dissolved in dry ether (50 ml.), and liquid ammonia (250 ml.) was added with stirring. Lithium (1·0 g.) was added in small pieces during 5 min. After a further 10 minutes' stirring absolute ethanol was added dropwise so that the solution became colourless after 15—20 min. The solvents were then evaporated and water was added to the residue. Extraction with ether and evaporation of the dried extract left a sticky solid which was dissolved in benzene and filtered through a small column of alumina. Removal of the benzene and crystallisation of the residue from methanol gave ergosta-4 : 22-dien-3-one (0·8 g.) as colourless needles, m. p. 129—130°, $\lambda_{max.}$ 241 mμ (log ε 4·23).

In this preparation, sodium could be used in place of lithium, a similar yield being obtained.

3-Oxobisnorcholan-22-al (V).—5β-Ergost-22-en-3-one (12 g.), dissolved in pure chloroform (250 ml.), was cooled to −70°, and treated with ozonised oxygen until the solution became faintly blue (this corresponded to an uptake of 1·0—1·05 mols. of ozone). Immediately, zinc dust (20 g.) was added, followed by glacial acetic acid (50 ml.), and the mixture was stirred at room temperature until it no longer gave a positive starch–iodide reaction (about 20 min.). The zinc residues were removed by filtration and the filtrate evaporated to a small bulk under diminished pressure. The residue was extracted with ether, and the extract was washed with potassium hydroxide solution (1%), water, and dried. Evaporation left *3-oxobisnorcholan-22-al* (9·2 g., 93%), as a white crystalline solid, m. p. 140—145°. This material was sufficiently pure for the next stage. A portion crystallised twice from *iso*propyl ether had m. p. 142—145°, $[\alpha]_D$ +24° (Found: C, 80·0; H, 10·5. $C_{22}H_{34}O_2$ requires C, 80·0; H, 10·4%).

3-Oxobisnorcholanic Acid.—5β-Ergost-22-en-3-one (4 g.), dissolved in chloroform (200 ml.), was cooled to 0° and treated with 2 mols. of ozone. The solvents were removed under reduced pressure and the residue was dissolved in a mixture of acetic acid (24 ml.) and ether (50 ml.). Zinc dust (4 g.) was added and the mixture stirred at room temperature for 30 min. After dilution with water and extraction with ether, the extract was dried and evaporated. The residue was dissolved in acetone (50 ml.) containing acetic acid (5 ml.), and a saturated solution of potassium permanganate in acetone (40 ml.) was added. After 2 hours' stirring the solution was acidified with dilute sulphuric acid. Sodium metabisulphite was then added until the mixture was colourless. Extraction with ether and crystallisation from methanol gave 3-oxobisnorcholanic acid (2·0 g., 58%), m. p. 178—180°, $[\alpha]_D$ +8°. (Budenandt and Mamoli, *Ber.*, 1935, **68**, 1854, give m. p. 184°, $[\alpha]_D$ +4·55°.) Reaction with diazomethane in ether gave the *methyl ester*, which crystallised from methanol as plates, m. p. 168—169°, $[\alpha]_D$ +20° (Found: C, 76·3; H, 10·1. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%).

3-Ethylenedioxy-5β-ergost-22-ene.—A mixture of 5β-ergost-22-en-3-one (6 g.), dry benzene (60 ml.) and ethylene glycol (12 ml.) was refluxed for 12 hr., in the presence of toluene-*p*-sulphonic acid (100 mg.), with constant removal of the water with barium oxide. After cooling, potassium hydroxide (0·5 g.) in methanol (10 ml.) was added, and the lower phase was discarded. The benzene extract was washed with water, dried, and evaporated. Crystallisation from methanol–ethyl acetate gave *3-ethylenedioxy-5β-ergost-22-ene* (6·0 g., 90%) as needles, m. p. 91—93°, $[\alpha]_D$ 0° (Found: C, 81·3; H, 11·2. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Methyl 3-Ethylenedioxybisnorcholanate.—3-Ethylenedioxy-5β-ergost-22-ene (2 g.), in chloroform (100 ml.) and pyridine (2 ml.), was treated with 2 mols. of ozone at 0°. The solvents were removed under reduced pressure and the residue was dissolved in ether (25 ml.) and acetic acid (12 ml.). Zinc dust (2 g.) was added, and, after 10 minutes' stirring, the zinc residues were removed by filtration. The acid fraction was extracted from the filtrate by shaking it with potassium

hydroxide solution (1%). The alkaline liquors were acidified with acetic acid, and the liberated acid was extracted with ether and worked up in the usual manner. The crude acid was methylated with diazomethane, and the ester was purified by chromatography on alumina. The benzene eluate yielded a crystalline solid. *Methyl* 3-*ethylenedioxybisnorcholanate* (0·72 g., 40%) separated from methanol as needles, m. p. 100—102°, $[\alpha]_D$ +10° (Found: C, 74·2; H, 9·8. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

Further degradation of the side chain of this compound with phenylmagnesium bromide yielded 3 : 22 : 22-*triphenylbisnorchola*-3 : 20(22)-*diene*, which crystallised from methanol as needles, m. p. 234—236°, $[\alpha]_D$ +373° (Found: C, 91·3; H, 9·0. $C_{40}H_{46}$ requires C, 91·2; H, 8·8%).

3-*Oxobisnorchol*-4-*en*-22-*al*.—A solution of ergosta-4 : 22-dien-3-one (5 g.) in chloroform (25 ml.) at −70° was treated with ozonised oxygen until 1 mol. had been absorbed. Zinc dust (7·5 g.) and acetic acid (50 ml.) were added and the mixture was shaken at room temperature until it no longer gave a positive starch–iodide test. Zinc residues were removed by filtration, and the filtrate was extracted with ether. After removal of the acid fraction with potassium hydroxide solution (1%), evaporation of the extract left a white solid which, after crystallisation from *iso*propyl ether, gave 3-oxobisnorchol-4-en-22-al (2·9 g.) as needles, m. p. 152—159°. A sample crystallised several times from *iso*propyl ether had m. p. 159—160°, $[\alpha]_D$ +88°. Heyl and Herr (*loc. cit.*) give m. p. 160—161°, $[\alpha]_D$ +82·5°.

Pregnane-3 : 20-*dione* (VII).—3-Oxobisnorcholan-22-al (2 g.) in acetic anhydride (20 ml.), containing fused sodium acetate (2 g.), was refluxed for 6 hr. in an atmosphere of nitrogen. The product, a light yellow gum, was treated in chloroform (100 ml.) with ozonised oxygen (1·4 mols.) at −70°. Zinc dust (6 g.) and glacial acetic acid (50 ml.) were added and the mixture was stirred at room temperature for 20 min. The filtered solution was evaporated, and the residue was dissolved in ether and washed with potassium hydroxide solution (1%), followed by water. Crystallisation from light petroleum (b. p. 40—60°) afforded pregnane-3 : 20-dione (1·08 g., 56%), m. p. 121—123°, $[\alpha]_D$ +109° (Found: C, 79·5; H, 10·1. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·2%).

22-*Piperidinobisnorchol*-20(22)-*en*-3-*one*.—A solution of 3-oxobisnorcholan-22-al (2 g.) in benzene (100 ml.), containing piperidine (0·8 ml.), was heated at the b. p. for 2·5 hr. The solvent was continuously dried with barium oxide during the reaction. After removal of the solvents, the product was chromatographed on alumina in benzene–light petroleum (1 : 10). The eluate, on evaporation, yielded a solid, which was crystallised several times from light petroleum, and then *iso*propyl ether, affording 22-*piperidinobisnorchol*-20(22)-*en*-3-*one* as needles, m. p. 111—130°, $[\alpha]_D$ +26°, $\lambda_{max.}$ 236 mμ (log ε 3·90) (Found: C, 81·7; H, 10·9. $C_{27}H_{43}ON$ requires C, 81·6; H, 10·9%). In an earlier communication (*Chem. and Ind.*, 1953, 1207) the m. p. and rotation of this compound were wrongly reported.

Pregnane-3 : 20-*dione from* 22-*Piperidinobisnorchol*-20(22)-*en*-3-*one*.—3-Oxobisnorcholan-22-al (2·8 g.) was converted into its 22-piperidino-derivative as described above, and the crude product was treated in pure chloroform (100 ml.) with ozonised oxygen at −70°, until a blue colour appeared. Zinc dust (4 g.) and acetic acid (50 ml.) were added and, after isolation in the usual manner, the product was chromatographed in benzene–light petroleum (1 : 1) on alumina. The first eluate afforded pregnane-3 : 20-dione (1·2 g., 54%), m. p. 119—122°, $[\alpha]_D$ +108°.

5β-*Ergost*-22-*en*-3α-*ol*.—(a) *From* 5β-*ergost*-22-*en*-3-*one*. (i) To a solution of potassium hydroxide (2 g.) in ethanol (200 ml.), Raney nickel sludge (2 ml.) was added, and the suspension was shaken in hydrogen until the catalyst was saturated. 5β-Ergost-22-en-3-one (2 g.) was then added and reduction continued until absorption was complete (122 ml.). After filtration, the solution was made acid with acetic acid and evaporated to dryness. Crystallisation from methanol afforded 5β-ergost-22-en-3α-ol (1·8 g., 90%), as needles, m. p. 149—150°, $[\alpha]_D$ −2° (Found: C, 83·9; H, 11·9. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·1%). Refluxing with acetic anhydride for 1 hr. gave 3α-acetoxy-5β-ergost-22-ene (93%), m. p. 115—116°, $[\alpha]_D$ +11° (Found: C, 81·0; H, 11·2. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·3%). Barton *et al.* (*loc. cit.*) give m. p. 149—150°, $[\alpha]_D$ −2°, for the alcohol and m. p. 114—115°, $[\alpha]_D$ +16°, for the acetate.

(ii) To a solution of 5β-ergost-22-en-3-one (2 g.) in dry ether (60 ml.) was added redistilled liquid ammonia (200 ml.) with stirring, followed by lithium (1 g.), in small pieces, during 5 min. Stirring was continued for 10 min., and dry ethanol (25 ml.) was then added dropwise during 10 min., by which time the solution became colourless. The ammonia was evaporated and water added. Isolation with ether and crystallisation from methanol gave 5β-ergost-22-en-3α-ol, m. p. 140—144°, which was converted directly into its acetate (1·6 g., 72%), m. p. 115—117°.

(b) *From ergosta-4 : 22-dien-3-one.* Ergosta-4 : 22-dien-3-one (5 g.) in ethanol (300 ml.), containing potassium hydroxide (3 g.), was hydrogenated over Raney nickel. Absorption ceased when 2 mols. of hydrogen had been taken up. After isolation with ether, a sample of the crude solid did not give a precipitate with digitonin. Crystallisation from methanol gave 5β-ergost-22-en-3α-ol (3·5 g., 69%), m. p. 146—149°.

(c) *From* iso*ergosterone.* By the method previously described, *iso*ergosterone (8·7 g.) was hydrogenated over Raney nickel. Absorption ceased after 3 mols. of hydrogen had been taken up. After isolation in the usual way, the crude product was crystallised from methanol, yielding 5β-ergost-22-en-3α-ol (7·0 g., 79%), m. p. 145—148°.

3α-*Acetoxybisnorcholan-22-al.*—3α-Acetoxy-5β-ergost-22-ene (12 g.) in chloroform (250 ml.) was ozonised at −70°. The solution became blue after 1 mol. of ozone had been absorbed. Isolation in the usual manner gave 3α-acetoxybisnorcholan-22-al (9·4 g., 92%), m. p. 125—128°. Crystallisation from *iso*propyl ether gave plates, m. p. 127—128°, $[\alpha]_D$ +33° (Found : C, 77·0; H, 10·4. Calc. for $C_{24}H_{38}O_3$: C, 77·0; H, 10·2%).

3α-*Acetoxybisnorcholanic Acid.*—(a) *Using an excess of ozone.* 3α-Acetoxy-5β-ergost-22-ene (2 g.) in chloroform (200 ml.) was treated with 2 mols. of ozone at 0—5°. The solvents were evaporated under reduced pressure and the ozonide was decomposed with zinc dust (2 g.) and acetic acid (12 ml.). Isolation of the steroid acid fraction, treatment with diazomethane, and crystallisation of the product from methanol gave the *methyl* 3α-*acetoxybisnorcholanate* (0·84 g., 46%) as plates, m. p. 109—112°, $[\alpha]_D$ +40° (Found : C, 73·7; H, 9·8. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

(b) *By ozone, followed by chromic acid oxidation.* 3α-Acetoxy-5β-ergost-22-ene (2 g.) in chloroform (75 ml.) was treated with 1·25 mols. of ozone at 0°. Zinc dust (3 g.) and acetic acid (100 ml.) were added and the mixture stirred for 1 hr. The solids were filtered off and the filtrate was evaporated to dryness. The residue was dissolved in acetic acid (50 ml.), and chromic acid (1 g.) in water (1 ml.) was added. The solution was allowed to remain at room temperature for 17 hr. After removal of the excess of chromic acid with methanol, the product was isolated with benzene. Crystallisation from methanol–water gave 3α-acetoxybisnorcholanic acid (1·1 g., 62%) as colourless blades, m. p. 220—223°, $[\alpha]_D$ +22° (Found : C, 73·8; H, 9·7. Calc. for $C_{24}H_{38}O_4$: C, 73·8; H, 9·8%). Treatment with diazomethane afforded the methyl ester, m. p. 109—112°.

3α-*Acetoxypregnan-20-one.*—3α-Acetoxybisnorcholan-22-al (4·46 g.) was heated at reflux under nitrogen for 5 hr. in acetic anhydride (36 ml.) containing anhydrous potassium acetate (0·07 g.). After isolation in the usual manner, the product was dissolved in dry ether (100 ml.), cooled to −35°, and treated with 1 mol. of ozone. The product was dissolved in light petroleum and purified by chromatography on alumina. Crystallisation from ether gave 3α-acetoxypregnan-20-one, as prisms, m. p. 100—101°, $[\alpha]_D$ +123° (Found : C, 76·2; H, 10·1. Calc. for $C_{23}H_{36}O_3$: C, 76·6; H, 10·1%).

3α-*Acetoxy-22-piperidinobisnorchol-20(22)-ene.*—3α-Acetoxybisnorcholan-22-al (6·4 g.) was refluxed under nitrogen for 2½ hr. in benzene (150 ml.) containing piperidine (5 ml.). Barium oxide was used to remove water from the distilling solvent. Removal of the solvent left a solid which, on crystallisation from methanol, gave 3α-acetoxy-22-piperidinobisnorchol-20(22)-ene (4·1 g., 54%) as plates, m. p. 106—110°. After recrystallisation from methanol, the analytical sample had m. p. 114—115°, $[\alpha]_D$ +47° (this rotation was wrongly recorded in the preliminary communication) (Found : C, 79·0; H, 10·6; N, 3·2. Calc. for $C_{29}H_{47}O_2N$: C, 78·8; H, 10·7; N, 3·2%).

3α-*Acetoxypregnan-20-one from* 3α-*Acetoxy-22-piperidinobisnorchol-20(22)-ene.*—A solution of the acetoxy-enamine (5·7 g.) in dry ether (200 ml.) was treated at −35° with ozonised oxygen until absorption of ozone was complete, as shown by analysis of the effluent gas. The product was chromatographed in light petroleum on alumina. The first fractions gave 3α-acetoxypregnan-20-one (2·7 g., 58%), which crystallised from ether as prisms, m. p. 100—101°, showing no depression on admixture with the previously prepared sample.

4-*Bromopregnane-3 : 20-dione.*—Pregnane-3 : 20-dione (1·0 g.) was dissolved in a mixture of methylene chloride (5 ml. saturated at room temperature with hydrogen bromide) and *tert.*-butanol (5 ml.), and cooled in ice. Bromine (0·50 g.) in a mixture of methylene chloride (5 ml.) and *tert.*-butanol (5 ml.) was added during 15 min. The solution was then set aside at room temperature until the colour was discharged. Extraction with ether gave a solid which crystallised from chloroform–ether, affording 4-bromopregnane-3 : 20-dione (0·65 g., 52%), m. p. 178—182°. Butenandt and Schmidt (*Ber.*, 1934, **67**, 1901) give m. p. 186—187°.

Progesterone.—4-Bromopregnane-3 : 20-dione (1·0 g.) was dissolved in a mixture of *tert.*-

butanol (50 ml.) and chloroform (30 ml.), and the air above the solution was displaced by nitrogen. Semicarbazide base (300 mg.) was added, and the solution was allowed to stand under nitrogen for a further 3 hr. After 0·5 hr., the solution became deep orange and later colourless. Solvents were removed under reduced pressure, and the residue was triturated with ethanol (15 ml.) and water (20 ml.). The solid semicarbazone (0·92 g.) had m. p. 234—236°, $[\alpha]_D$ +192° (*c*, 0·2 in 1 : 1 chloroform–*tert.*-butanol), $\lambda_{max.}$ 270 mμ (log ε 4·46).

The semicarbazone was dissolved in acetic acid (15 ml.), containing water (5 ml.) and *p*-hydroxybenzaldehyde (1·6 g.), and sealed under nitrogen for 24 hr. Isolation with ether gave a product which was dissolved in benzene and chromatographed on alumina. A benzene–ether eluate gave progesterone (0·30 g., 38%), which crystallised from light petroleum as blades, m. p. and mixed m. p. 127—129°, $[\alpha]_D$ +220°.

The authors are indebted to Mr. D. J. Outred for assistance with the experimental work.

WALTON OAKS EXPERIMENTAL STATION, VITAMINS LIMITED,
DORKING ROAD, TADWORTH, SURREY. [*Received, March 30th*, 1954.]

NOTES.

The Exchange of Iodine Atoms between Iodine and Methyl Iodide in the Temperature Range 150—375°.

By DOUGLAS CLARK, H. O. PRITCHARD, and A. F. TROTMAN-DICKENSON.

[Reprint Order No. 4863.]

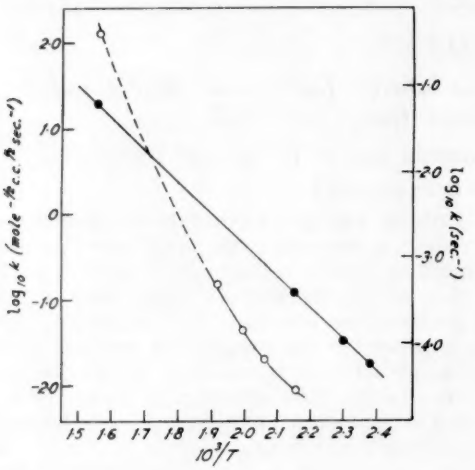
OGG and POLANYI (*Trans. Faraday Soc.*, 1935, **31**, 482) showed that the reaction between iodine atoms and *sec.*-butyl iodide leads to optical inversion of the butyl iodide molecule. They found that below 200° the racemisation was a heterogeneous reaction of low activation energy (8 kcal./mole), but that in the temperature range 240—280° the homogeneous inversion by iodine atoms predominated because of its considerably higher activation energy (32·2 kcal./mole); the investigation was complicated, however, by the fact that at these temperatures the butyl iodide molecule is unstable. In an attempt to gain a better understanding of the factors affecting these inversion reactions, we have studied the exchange of ^{131}I atoms between iodine and methyl iodide vapours, hoping to follow the very simplest example of an inversion reaction, *i.e.*,

The reaction was studied over the temperature range 185—250° in a Pyrex bulb of about 1 l. capacity: known pressures of methyl iodide (*ca.* 50 cm.) and of radio-iodine (*ca.* 1 cm.) were introduced into the bulb (at constant temperature; thermostat) and allowed to react; after a known time, the reaction was terminated by condensation of the iodine–methyl iodide mixture in liquid air. The reaction products were shaken with mercury and a little acetone to remove free iodine, and the remaining mixture of methyl iodide and acetone was distilled off and made up to a standard volume with acetone; the mercuric iodide left was dissolved in 10% sodium iodide solution and made up to the standard volume with water. The extent to which the reaction had occurred was then determined from the ratio of the γ-ray activities of the two solutions (tests showed only a minute difference between the γ-ray assay obtained when a known quantity of iodine was counted in either aqueous or acetone solution).

It was found that the rate of transference of radioactivity from the iodine to the methyl iodide was represented by the equation Rate $= k[MeI][I_2]^{\frac{1}{2}}$, as is required for the inversion reaction, but that a plot of log k against $1/T$ was not a straight line (see Figure), suggesting that the reaction might be partly heterogeneous. When the reaction vessel was packed with Pyrex tubes, increasing the surface to volume ratio by a factor of about 8, the reaction rate increased 30-fold; the reaction remained of first order in methyl iodide concentration, but became independent of iodine concentration over a three-fold variation. The Arrhenius plot of these first-order, heterogeneous rate constants gives a straight line,

roughly parallel to the lower portion of the plot for the unpacked vessel, corresponding to an activation energy of about 17 kcal./mole.

By analogy with Ogg and Polanyi's results, we assumed that the reaction occurred by two mechanisms, one heterogeneous having an activation energy of about 17 kcal./mole, the other homogeneous having a higher activation energy; if this were the case, higher temperatures would favour the latter reaction, and in order to try to isolate this reaction, experiments were carried out at 375° in a conventional flow pyrolysis apparatus (Leigh, Sehon, and Szwarc, *Proc. Roy. Soc.*, 1951, *A*, **209**, 97). The reactants were introduced into the reaction zone, methyl iodide vapour at about 8 mm. pressure being used as a carrier for the iodine; the rate of flow of methyl iodide was adjusted to give a contact time of about $\frac{3}{4}$ sec., and the iodine pressure was adjusted to give about the same ratio of $[MeI]/[I_2]$ as in the static experiments. A point representing the mean of several bimolecular rate constants is shown in the Figure as a continuation of the Arrhenius curve, since the surface to volume ratios for the two unpacked reaction vessels were not very



Arrhenius plots for the exchange of radio-iodine with methyl iodide:
○ *in an unpacked reaction vessel,*
● *in a packed reaction vessel.*

different. However, packing the reaction vessel showed that even at this temperature the reaction was largely heterogeneous, and the heterogeneous rate was still dependent only on the methyl iodide concentration. Two types of packing were used in testing for heterogeneity in the flow system. In one set of experiments the reaction zone was packed completely with short lengths of Pyrex tube, resulting in a 6-fold increase in surface to volume ratio; the rate of the reaction increased by a factor of 6 as a result. The rate constants obtained were scaled up in the ratio of 8 to 6 to allow for the disparity in surface to volume ratios of the two packed reaction vessels, and the mean point thus obtained was found to lie very close to the continuation of the Arrhenius plot for the heterogeneous reaction observed at lower temperatures; the best line through all these points represents an activation energy of 17·0 kcal./mole.

A second type of packing, which has sometimes been used in kinetic studies, was also tried: enough quartz fibre to increase the surface area of the effective reaction zone by a factor of 4—5 was introduced into the vessel; the volume of this packing was quite small and it lay on the floor of the reaction vessel, occupying only about one-fifth of the volume of the reaction zone. No increase in reaction rate was observed under these conditions, suggesting that with contact times as short as those used here, the main body of the gas streams through the reaction vessel without coming into contact with the fibre packing. Such observations must cast some doubt on the interpretation of those kinetic measurements in which this type of packing was used, as it seems only to provide a stringent test for heterogeneity when it is distributed throughout the whole cross-section of the reaction zone.

These experiments show that it is not possible to isolate the reaction of higher activation

energy, which probably represents the inversion of methyl iodide by iodine atoms (because of the nature of the kinetics in the unpacked vessels) at temperatures at which methyl iodide is stable; the only conclusion we can draw is that, from the slope of the upper portion of the Arrhenius curve, the activation energy is certainly not less than the 32·2 kcal./mole observed by Ogg and Polanyi for *sec.*-butyl iodide.

We thank Professor Geoffrey Gee, F.R.S., for his interest, Manchester University for the award of an I.C.I. Fellowship to one of us (A. F. T.-D.), and the D.S.I.R. for the award of a maintenance grant (D. C.).

CHEMISTRY DEPARTMENT, MANCHESTER UNIVERSITY.
[Present address (A. F. T.-D.): E. I. DUPONT DE NEMOURS AND CO., NIAGARA FALLS.]
[*Received, December 4th,* 1953.]

The Magnetic Susceptibility of Lanthanum.

By O. M. HILAL and F. A. SALEH.

[Reprint Order No. 5050.]

EGYPTIAN monazite, after separation of thorium and most of the cerium, was split into four fractions by the sodium nitrite separation (Hilal and El-Abbady, *J.*, 1952, 2935). The tail fraction contained most of the lanthanum. Its apparent atomic weight was 141·51 and bands of praseodymium, neodymium, and samarium were observed in the visible region. It was converted into nitrate and fractionated by the nitrite precipitation (*loc. cit.*) 179 times in 14 series, coloured head fractions being discarded. The last series was split into 16 fractions. The χ value of the lanthanum ion was determined and the last nine fractions gave the same value, within the experimental error, so they were mixed together (80·6 g. of oxide) and fractionally precipitated by ammonia carried in a current of air (Hilal and Sugden, *J.*, 1949, 135). After systematic separation involving 23 precipitations, 12 fractions were obtained, representing 21·2% of the crude lanthana. The magnetic susceptibility of the lanthanum ion from these fractions showed no substantial change from the previous values and so they were regarded as pure lanthana; they had $10^6\,\chi^{20}_{La^{+++}} = -0{\cdot}17 \pm 0{\cdot}01$.

Two determinations of the apparent atomic weight of this oxide gave 138·97, 138·88; mean 138·92. The emission spectrum of the pure oxide, a copper–graphite arc and a small quartz spectrograph being used, showed no lines other than those of lanthanum. In particular the persistent lines of cerium and praseodymium were absent.

The nitrite precipitation method for the purification of lanthanum is therefore satisfactory when the yield and purity are compared with those obtained on precipitation by air-borne ammonia (Vickery, *J.*, 1952, 2506), and cerium, if present, is concentrated in the head fractions more easily than by the latter method.

For comparison, a solution of mixed rare-earth nitrates (80 g. of oxide/l.), containing a small percentage of cerium, was fractionated by both methods. In the first, the filtrate after the fourth fraction was found to be free from cerium, and contained 21% of the total weight of the original oxide, whereas by the second method a cerium-free filtrate was not obtained until after the fifth fraction, and contained 12%. Moreover, cerium is automatically eliminated during the nitrite precipitations, as its precipitate does not easily dissolve in cold dilute nitric acid.

The precipitate obtained on treating chemically pure lanthanum nitrate solution with sodium nitrite, as detailed above, contained La_2O_3, 71·29; N_2O_3, 16·56; H_2O (by diff.), 12·15%. The absence of N_2O_5 was confirmed colorimetrically. The composition is therefore $La_2O_3,N_2O_3,3H_2O$, the ratio $La_2O_3 : N_2O_3$ being the same as that found by Sherwood (*J. Amer. Chem. Soc.*, 1944, **66**, 1228).

The apparent atomic weight was determined by Hilal and Sugden's method (*loc. cit.*) within 0·1 unit. The titration was carried out potentiometrically and approximately 0·5N-ammonium oxalate solution was used as a precipitant, as its pH coincides with the pH at the neutralisation point.

The magnetic susceptibility was determined at 20° $\pm$ 0·02° by Gouy's method with the specimen in a fixed position (Hilal and Fredericks, *J.*, 1954, 785), Hilal and Sugden's procedure (*loc. cit.*) being used. Strict additivity of the susceptibilities of the constituents in a chloride solution being assumed, the χ value of the La^{+++} could be calculated. The value of $10^6\,\chi_{Soln.}$ could be determined to within 0·001 and the consequent error in $10^6\,\chi_{La^{+++}}$ was not more than $\pm$0·01.

ALEXANDRIA UNIVERSITY, MOHARRAM BAY, ALEXANDRIA. [*Received, January 22nd,* 1954.]

2 : 2′ : 4 : 4′ : 5 : 5′-*Hexamethoxydiphenyl.*

By W. I. Taylor.

[Reprint Order No. 5138.]

2 : 2′ : 4 : 4′ : 5 : 5′-Hexamethoxydiphenyl has been isolated as a by-product in the preparation of large quantities of 1 : 2 : 4-trimethoxybenzene by methylation of crude methoxyquinol. Since methylation of purified methoxyquinol afforded no hexamethoxydiphenyl, the latter must be derived mainly from the unknown 2 : 2′ : 5 : 5′-tetrahydroxy-4 : 4′-dimethoxydiphenyl formed during the alkaline hydrogen peroxide oxidation of the vanillin to methoxyquinol. We have not, however, been able to isolate pure tetrahydroxydimethoxydiphenyl from the tar left after the methoxyquinol had been purified.

Experimental.—Crude methoxyquinol (350 g.) (Dakin, *Amer. Chem. J.*, 1909, **42**, 477) was methylated by methyl sulphate and alkali. The crude 1 : 2 : 4-trimethoxybenzene was extracted with ether, which was washed with water until neutral and dried (Na_2SO_4). After the ether had been removed and about one-third of the 1 : 2 : 4-trimethoxybenzene (b. p. 96°/0·4 mm.) had been distilled off, there appeared in the distillation flask a voluminous crystalline precipitate which was filtered off and washed with ethanol, to yield pure 2 : 2′ : 4 : 4′ : 5 : 5′-hexamethoxydiphenyl (12 g.), m. p. and mixed m. p. 176—177° (Found : C, 64·4; H, 6·7; MeO, 55·6. Calc. for $C_{18}H_{22}O_6$: C, 64·5; H, 6·6; MeO, 55·6%), ultra-violet absorption maximum in 95% EtOH at 298 mμ (log ε 4·06).

Chemical Laboratories, University of New Brunswick. [*Received, February 20th*, 1954.]

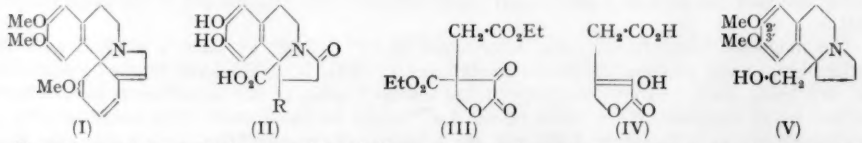
Condensation of α-Keto-acids with 2-3′ : 4′-Dihydroxyphenylethylamine.

By J. S. Little, A. G. Smith, W. I. Taylor, and B. R. Thomas.

[Reprint Order No. 5139.]

Synthesis by Belleau (*J. Amer. Chem. Soc.*, 1953, **75**, 5765) of the tetracyclic ring system present in some of the *Erythrina* alkaloids, *e.g.*, erysodine (I) (Karmack, McKusick, and Prelog, *Helv. Chim. Acta*, 1951, **34**, 1601), prompts us to report some work carried out some time ago.

Hahn and Stiehl (*Ber.*, 1936, **69**, 2645) showed that α-oxoglutaric acid reacted readily with 2-3′ : 4′-dihydroxyphenylethylamine hydrochloride in aqueous solution to yield (II; R = H) and we attempted to extend this reaction to the preparation of (II; R = $[CH_2]_2{\cdot}CO_2H$) from which erysodine (I) might be elaborated. For this purpose β-oxaloadipic acid was required. Ethyl β-iodopropionate and diethyl sodiooxalosuccinate afforded diethyl β-ethoxalyl-β-ethoxycarbonyladipate which, however, on acid hydrolysis furnished butane-1 : 2 : 4-tricarboxylic acid : hindrance of the tertiary ethoxycarbonyl group allows more rapid hydrolysis and consequent elimination of oxalo-group. In spite of this, successful preparations of disubstituted pyruvic acids have been recorded by this general route (*e.g.*, 3-methyl-2-oxopentanoic acid from ethyl ethoxalylpropionate; Mebus, *Monatsh.*, 1905, **26**, 483). The method developed by Schreiber (*Ann. Chim.*, 1947, **2**, 84) for the preparation of α-keto-acids from aliphatic α-ethoxalyl esters *via* the internal anhydrides was applied to the present case but the only tractable product was the above-mentioned tricarboxylic acid. We were also unable to make β-ethyl-α-oxoglutaric acid from ethoxalylsuccinic ester by similar methods : instead, ethylsuccinic acid was formed. A model β-monosubstituted α-oxoglutaric acid was prepared to see whether a disubstituted pyruvic acid of this type would condense with 2-3′ : 4′-dihydroxyphenylethylamine.



(I) (II) (III) (IV) (V)

Reaction of formaldehyde with diethyl ethoxalylsuccinate yielded the lactone (III) which after acid hydrolysis furnished β-carboxymethyl-α-oxobutyro-γ-lactone whose infrared spectrum indicated that the keto-group was completely enolised (cf. IV). However

this did not condense with 2-3′ : 4′-dihydroxylphenylethylamine. Hahn, Bärwald, Schales, and Werner (*Annalen*, 1935, **520**, 107) found no reaction to occur with either trimethylpyruvic acid or phenylglyoxylic acid and suggested that for condensation to take place the α-keto-group must be enolisable; the lack of reactivity of our acid (IV) must be due to another cause. We were also unable to effect condensation of the amine, under neutral or strongly acidic conditions, with *cyclo*hexanone, ethyl 2-oxo*cyclo*hexanecarboxylate or 2-oxo*cyclo*hexylglyoxylate, or 2-oxo*cyclo*hexylacetic acid.

The lactam (II; R = H) has been methylated with diazomethane and reduced directly with lithium aluminium hydride to 9-hydroxymethyl-2′ : 3′-dimethoxy-7 : 8-benzopyrrocoline (V) whose physiological properties will be described elsewhere.

Experimental.—Butane-1 : 2 : 4-tricarboxylic acid. Condensation of ethyl β-iodopropionate (43·4 g.) and diethyl sodio-oxalosuccinate (54 g.) furnished crude diethyl β-ethoxalyl-β-ethoxycarbonyladipate (50·6 g.), b. p. 165—167°/2 mm. (Found: C, 55·6; H, 7·4; OEt, 49·2. Calc. for $C_{17}H_{26}O_9$: C, 54·6; H, 7·0; 4OEt, 48·1%). The crude ester (20 g.) was refluxed overnight with 20% sulphuric acid (200 c.c.), then extracted exhaustively with ether, to yield crude butane-1 : 2 : 4-tricarboxylic acid (12·5 g.) which after two crystallisations from ether–chloroform melted constantly at 120—122° (lit., 116—119°) (Found: C, 43·9; H, 5·2. Calc. for $C_7H_{10}O_6$: C, 44·2; H, 5·3%). The crude ester (9·7 g.) and sulphuric acid (10 g.) were set aside for 2 weeks after which the solution was diluted with four volumes of water and saturated with hydrogen chloride under reflux. Cooling and exhaustive extraction with ether gave a crude oily acid (5·6 g.) which afforded pure butane-1 : 2 : 4-tricarboxylic acid, m. p. 120—121°, after several crystallisations from ether–chloroform (Found: C, 43·9; H, 5·3%). From the mother-liquors from both acid hydrolyses, and from those of other experiments, no α-keto-acid could be isolated.

Ethylsuccinic acid. Condensation of ethyl bromide with diethyl sodioethoxalylsuccinate afforded diethyl ethylethoxalylsuccinate (50 g.), b. p. 140—144°/1·5 mm., which with 10% sulphuric acid furnished, after ether-extraction, ethylsuccinic acid (17·6 g., 90%), m. p. 98° (lit., 98°) (Found: C, 49·2; H, 6·9. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 6·9%). No other compounds could be isolated and the mother-liquors gave a negative test for ketones with 2 : 4-dinitrophenylhydrazine.

β-*Carboxymethyl-α-oxobutyro-γ-lactone* (IV). Potassium carbonate (2·5 g.) was added portionwise during 1 hr. to a cooled well-stirred mixture of formaldehyde (3 c.c. of 36% solution) and diethyl ethoxalylsuccinate (10 g.) in water (15 c.c.). The clear solution was saturated with ammonium sulphate, extracted three times with ether (50 c.c.), dried (Na_2SO_4), and concentrated to dryness, to yield on distillation a low-boiling fraction (not further investigated) and a crude lactone (III) (4·5 g.) as a viscous oil, b. p. 140—145°/2·5 mm. (strong bands in the carbonyl region at 1810 cm.$^{-1}$, γ-lactone; 1750 cm.$^{-1}$, keto-group in a five-membered ring; and 1735 cm.$^{-1}$, carboxylic ester). The lactone (III) (2·5 g.) was heated at 110° for 3 hr. in acetic acid (10 c.c.), water (7 c.c.), and hydrochloric acid (10 c.c.), then extracted with ether to furnish a crystalline product which after two crystallisations from ethyl acetate gave β-*carboxymethyl-α-oxobutyro-γ-lactone* (280 mg.), m. p. 155—157° (Found: C, 45·7; H, 4·0. $C_6H_6O_5$ requires C, 45·6; H, 3·8%) (infra-red bands at 1710 and 1735 cm.$^{-1}$ due to carbonyl stretching frequencies of a carboxyl group, and an αβ-unsaturated γ-lactone slightly lower than usual because of the 2-hydroxy-group).

9-*Hydroxymethyl-2′ : 3′-dimethoxy-7 : 8-benzopyrrocoline* (V). The lactam (II; R = H) (760 mg.) was kept with excess of diazomethane in methanol–ether, then evaporated *in vacuo*. The gummy product was taken up in a little methanol, absorbed into a filtration accelerator pad, dried *in vacuo*, then extracted (Soxhlet) into a solution of lithium aluminium hydride in absolute ether. After addition of ethyl acetate, the ethereal solution was shaken vigorously with 10% sodium hydroxide solution and with water, dried (Na_2SO_4), and concentrated, to furnish an oily base purified as its *picrate* (730 mg.), m. p. 201—202° (Found: C, 51·1; H, 5·0; N, 11·2. $C_{21}H_{24}O_{10}N_4$ requires C, 51·2; H, 4·9; N, 11·4%). The *base*, regenerated from the picrate, was an oil (Found, on a sample sublimed at 140°/0·5 mm.: C, 68·5; H, 8·2; N, 5·5. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·0; N, 5·3%).

We are indebted to the National Research Council of Canada, for a grant and for a N.C.R. studentship (to J. S. L.), and for a N.R.C. post-doctorate fellowship (to B. R. T.).

CHEMICAL LABORATORIES, UNIVERSITY OF NEW BRUNSWICK. [*Received, February 20th*, 1954.]

The Methanolysis of Some Acetyl Derivatives of Cevine.

By W. J. Rosenfelder.

[Reprint Order No. 5164.]

The methanolysis of esters of the tertiary steroidal alkaloids has been widely reported (*inter al.*, Fried, White, and Wintersteiner, *J. Amer. Chem. Soc.*, 1950, **72**, 4621; Fried, Numerof, and Coy, *ibid.*, 1952, **74**, 3041; Kupchan and Deliwala, *ibid.*, 1952, **74**, 3202; Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1942). In principle this methanolysis could be a selective neighbouring group effect (cf. Winstein *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 2297, and earlier papers there cited) or simply a consequence of the basicity of the medium due to the tertiary nitrogen atom. In either event, the reaction should be inhibited by quaternisation of the nitrogen atom: this was shown to be true, it being observed that whereas cevine di- and tetra-acetate were readily methanolysed, conversion into a methiodide or into an *N*-oxide afforded a product that was stable to aqueous methanol. However, it was found that addition of one mole of triethylamine to cevine tetra-acetate methiodide in methanol caused the methanolysis to proceed again quite rapidly, thus indicating that it is merely the basic property of the tertiary nitrogen atom of the cevine ester that is necessary to catalyse the reaction.

An interesting observation in the reaction of cevine di- and tetra-acetate with hydrogen peroxide (cf. Freund, *Ber.*, 1904, **37**, 1946; Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1270, for the preparation of cevine and cevagenin *N*-oxides) was the loss of one acetate residue giving cevine monoacetate *N*-oxide and cevine triacetate *N*-oxide, respectively. The structures of these two compounds, which had been assigned on the basis of their acetyl values, were confirmed by conversion into the *N*-oxides of cevine di- and tetra-acetate. This conversion was readily effected by mild treatment with acetic anhydride, authentic samples of the di- and tetra-acetate *N*-oxides being obtained by the action of one mol. of perphthalic acid on the corresponding tertiary bases. The *N*-oxides of all these four acetates of cevine proved to be stable to aqueous methanol.

Experimental. Values of $[\alpha]_D$ have been approximated to the nearest degree. Cevine has $[\alpha]_D$ $-19°$ (*c*, 2·00 in methanol). Acetyl values were determined by the method described in Roth, "Quantitative Organic Micro-analysis of Fritz Pregl," 3rd English Edn., J. and A. Churchill Ltd., p. 191 *et seq.*

The methanolysis of cevine diacetate. Cevine diacetate (Freund, *Ber.*, 1904, **37**, 1946; Barton and Eastham, *J.*, 1953, 424) (0·1242 g.) was dissolved in 90% aqueous methanol (3 ml.). The initial value of $[\alpha]_D$ was $-1°$, changing to $-12°$ (2 days), $-13·5°$ (4 days), and $-15°$ (9 days) at room temperature.

The methanolysis of cevine tetra-acetate. Cevine tetra-acetate (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1270; Barton and Eastham, *loc. cit.*) (0·0196 g.) was dissolved in 90% aqueous methanol (2 ml.). The initial value of $[\alpha]_D$ was $+41°$, changing to $+26°$ (3 days) and $+20°$ (9 days) at room temperature.

Cevine diacetate N-*oxide.* Cevine diacetate (500 mg.) was dissolved in pure dry dioxan (10 ml.) and benzene (7 ml.), and a solution of perphthalic acid (110% of theory for 1 mol.) in ether was added. The reaction was followed by withdrawing 1-ml. samples of the solution from time to time, adding an excess of aqueous potassium iodide solution, and titrating the iodine liberated against 0·01N-sodium thiosulphate solution. After about 40 min. at room temperature, one mol. of perphthalic acid had reacted; the solution was taken up in a large volume of chloroform, washed with dilute ammonia, water, dilute acetic acid, and again with water, and was then dried and distilled. The residue was twice crystallised from aqueous methanol. *Cevine diacetate* N-*oxide* formed prisms, m. p. 219—220° (decomp.), $[\alpha]_D$ $-1°$ (*c*, 2·46), from 90% aqueous methanol (Found: C, 59·1; H, 7·8; Ac, 11·8. $C_{31}H_{47}O_{11}N,H_2O$ requires C, 59·3; H, 7·9; Ac, 13·7%).

No change in rotation was observed at room temperature in a solution of cevine diacetate *N*-oxide (0·0734 g.) in 3 ml. of 90% aqueous methanol during 3 days, and on concentration of the solution, prisms of cevine diacetate *N*-oxide, m. p. and mixed m. p. 219—220° (decomp.), were recovered.

Cevine tetra-acetate N-*oxide* (with Dr. J. S. Fawcett). Cevine tetra-acetate (420 mg.) was treated with one mol. of perphthalic acid in an analogous manner to the diacetate (see above).

The product after two recrystallisations from aqueous methanol afforded needles of *cevine tetra-acetate N-oxide*, m. p. 223—226° (decomp. and softening above 215°), $[\alpha]_D$ +18° (*c*, 1·46), +20° (*c*, 1·87) in chloroform; $[\alpha]_D$ +40° (*c*, 1·86) in 90% aqueous methanol (Found: C, 57·1; H, 7·5; Ac, 24·5. $C_{35}H_{51}O_{13}N,2H_2O$ requires C, 57·6; H, 7·6; Ac, 23·6%). A solution (0·0558 g.) in aqueous methanol (90%; 3 ml.) still had a specific rotation of +40° after 3 days at room temperature.

Cevine monoacetate N-oxide. A suspension of cevine diacetate (300 mg.) in 30% hydrogen peroxide (1·5 ml.) was warmed on a steam-bath for 3—5 min. The resulting solution was evaporated to dryness *in vacuo* and the residue taken up in hot ethanol, and the solution treated with charcoal and concentrated, and a little water added. After 5 days crystals (130 mg.) were obtained which after one more recrystallisation from aqueous ethanol afforded *cevine monoacetate N-oxide*, m. p. 264—265° (decomp. above 230°), $[\alpha]_D$ −15° (*c*, 2·19 in 90% MeOH–H_2O) (Found: C, 59·1; H, 8·1; N, 2·1; Ac, 8·1. $C_{29}H_{45}O_{10}N,H_2O$ requires C, 59·5; H, 8·1; N, 2·4; Ac, 7·4%). After 3 days at room temperature a solution in 90% aqueous methanol still had $[\alpha]_D$ −15° and on concentration *in vacuo* of this solution cevine monoacetate *N*-oxide, m. p. and mixed m. p. 262—263° (decomp. above 225°), was recovered.

Mild acetylation of cevine monoacetate N-oxide. Cevine monoacetate *N*-oxide (65 mg.) and acetic anhydride (1 ml.) were warmed on a steam-bath for 5 min. Water was now added and the solution evaporated to dryness *in vacuo*. The product, upon recrystallisation from aqueous methanol, had m. p. 219—220° (decomp.), $[\alpha]_D$ −2° (*c*, 1·34 in 90% MeOH–H_2O) and did not depress the m. p. of an authentic sample of the diacetate *N*-oxide.

Cevine triacetate N-oxide. Cevine tetra-acetate (300 mg.) was treated with 30% hydrogen peroxide (1·5 ml.) in a manner analogous to the conversion of cevine diacetate into cevine monoacetate *N*-oxide (see above). The product after one crystallisation from aqueous methanol and one from aqueous ethanol gave *cevine triacetate N-oxide*, m. p. 230—232° (decomp., after softening at 217°), $[\alpha]_D$ +29° (*c*, 4·00 in 90% MeOH–H_2O) (Found: C, 57·2; H, 7·6; N, 2·1; Ac, 17·4. $C_{33}H_{49}O_{12}N,2H_2O$ requires C, 57·6; H, 7·6; N, 2·0; Ac, 18·8%). After four days at room temperature a solution of cevine triacetate *N*-oxide (0·0873 g.) in 90% aqueous methanol (5 ml.) still had $[\alpha]_D$ +29°.

Mild acetylation of cevine triacetate N-oxide. The product of reaction of cevine triacetate *N*-oxide (24 mg.) and acetic anhydride (1 ml.) was worked up by dilution with water and concentration to dryness. The residue, upon recrystallisation from aqueous methanol, did not depress the m. p. of an authentic sample of cevine tetra-acetate *N*-oxide, and had $[\alpha]_D$ +20° (*c*, 1·77 in $CHCl_3$).

Cevine tetra-acetate methiodide. Cevine tetra-acetate (300 mg.) was dissolved in anhydrous acetone (3 ml.), and methyl iodide (3 ml.) added. After 24 hr. at room temperature in a stoppered flask, the solution was evaporated to dryness *in vacuo* at room temperature. The residue was crystallised twice from water (2—3 ml.) affording *cevine tetra-acetate methiodide*, m. p. 227—227·5° (decomp.), $[\alpha]_D$ +37° (*c*, 1·75), +36° (*c*, 1·38) in 90% aqueous methanol (Found: C, 48·7; H, 7·0; N, 1·7; I, 14·2. $C_{36}H_{54}O_{12}NI,4H_2O$ requires C, 48·5; H, 7·0; N, 1·6; I, 14·2%). A solution of cevine tetra-acetate methiodide (0·0873 g.) in 90% aqueous methanol (5 ml.) had $[\alpha]_D$ +37° (zero time), +36° (9 days at room temperature). On concentration *in vacuo* and crystallisation from aqueous methanol, cevine tetra-acetate methiodide, m. p. and mixed m. p. 227—227·5° (decomp., after softening at 225°) was recovered.

Methanolysis of cevine tetra-acetate methiodide in presence of 1 mol. of triethylamine. Cevine tetra-acetate methiodide (0·0804 g.) was dissolved in methanol (4 ml.), and a solution (1 ml.) of triethylamine (0·125 ml. in 10 ml. of water) added. The mixture was set aside at room temperature; the variation of the specific rotation with time is given in the following table:

Time	18 hr.	24 hr.	4 days	6 days	8 days	12 days	20 days	28 days
$[\alpha]_D$	+24°	+20·5°	+14°	+9°	+7°	+4°	−1°	−3°

After 28 days the solution was evaporated to dryness *in vacuo* and the residue recrystallised from water giving cevine methiodide (Freund and Schwarz, *J. pr. Chem.*, 1917, **96**, 236; Jacobs and Craig, *J. Biol. Chem.*, 1938, **125**, 625; Barton and Eastham, *loc. cit.*), m. p. and mixed m. p. with an authentic sample, kindly supplied by Professor D. H. R. Barton, F.R.S., 247—252° (decomp.).

The author is grateful to Professor D. H. R. Barton, Dr. C. J. W. Brooks, and Dr. J. S. Fawcett for their interest in this work.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, February 26th*, 1954.]

The Surface Tension of Antimony Pentafluoride.

By D. R. Hub and P. L. Robinson.

[Reprint Order No. 5176.]

Antimony pentafluoride differs remarkably in both physical and chemical properties from arsenic pentafluoride. Its boiling point and liquid density (Ruff, Graf, Heller, Knoch, and Plato, *Ber.*, 1904, **37**, 673; 1906, **39**, 4310), (appreciable) electrical conductivity and (abnormally high) viscosity (Woolf and Greenwood, *J.*, 1950, 2200), vapour pressure and liquid density (Schair and Schurig, *Ind. Eng. Chem.*, 1951, **43**, 1624) have been measured. Vapour density measurements made here (G. J. Falconer) by a modified Dumas method gave at 180° a value of 296, suggesting a molecular weight of 592 and a molecular association corresponding to $(SbF_5)_{2\cdot7}$. Other measurements made here indicated a complexity approximating to $(SbF_5)_3$ at 150° and $(SbF_5)_2$ at 250°. Attempts were made to determine the surface tension of the liquid by measuring the differential capillary rise in a closed system (Mills and Robinson, *J.*, 1927, 1823), but the result was too low to be considered probable, owing to the high viscosity and possibly also to the angle of contact. So far as we know the surface tension of antimony pentafluoride has not been otherwise measured, and we now give values obtained between 0° and 138° with a maximum bubble pressure apparatus (Sugden, *J.*, 1922, **121**, 858; Mills and Robinson, *J.*, 1931, 1629) suitably modified to protect a hygroscopic liquid and using dried air.

T (°c)	0·5	1·0	1·75	2·3	18·9	19·6	39·8	82·6	106·3	119·5	138·4
γ (dynes cm.$^{-1}$)	51·5	47·0	50·6	48·7	45·7	44·5	39·9	31·8	28·4	26·4	23·1

The parachor derived from these surface tensions, $(P)_{obs.} = 169{\cdot}5$, is low compared with that calculated, $\Sigma(P) = 194{\cdot}5$, from Sugden's data ("The Parachor and Valency," Routledge, London, 1930, p. 181). That calculated of the basis of Walden's boiling-point rule, $P_W = 185{\cdot}8$, is closer to the theoretical value. The low figure found above conforms with the fact that liquid antimony pentafluoride is highly associated.

The Katayama plot of $\gamma/(D-d)^{2/3}$ against T is slightly curved which, again, is due to association; the slope of the best straight line through the points between 60° and 138° gives the critical temperature $T_c = 324{\cdot}6°$.

Experimental.—Preparation. Antimony trioxide, dried just below its melting point in an evacuated Pyrex glass tube, was fluorinated with a 4 : 1 mixture of fluorine and nitrogen. It was thrice fractionated with rejection on each occasion of head and tail fractions.

Measurement. The resulting liquid was distilled into the all-glass surface-tension vessel in which the jets, protected from atmospheric moisture by guard traps cooled in liquid oxygen, were sealed in position. The vessel was mounted in a bath at the required temperature, and the difference in pressure needed to produce bubbles at the respective jets was measured with a water-manometer. The surface tension was calculated by Sugden's method (*J.*, 1922, **121**, 858; 1924, **125**, 27), but as neither of his approximations can be used, owing to the low specific cohesion, a, his original method was employed which involved calculation of further values for $X/r_{min.}$, namely, 0·3640, 0·3484, 0·3351 corresponding respectively to values of $r/a = 1{\cdot}70$, 1·80, 1·88. The last is the highest value for which the tables of Bashforth and Adams ("An Attempt to Test the Theory of Capillary Action," Cambridge Univ. Press, 1883) can be used.

It was difficult to obtain consistent pressures at low temperatures owing to the high viscosity of the liquid, but a rapidly-tapering jet was better than one of uniform bore. Some hours were allowed at these temperatures for the attainment of thermal equilibrium in the sluggish liquid which was meanwhile gently stirred by a stream of air. The maximum bubble pressure was taken as that required to produce the first bubble after a momentary interruption of a stream of bubbles: bubbles subsequent to the first tended to merge into one another with a consequent fall in pressure. Even despite these precautions the readings for the supercooled liquid, *i.e.*, the first four above, are scattered.

The authors acknowledge a maintenance grant from the Department of Scientific and Industrial Research to one of them (D. R. H.) and thank Imperial Chemical Industries Limited, General Chemicals Division, Widnes, for the use of the necessary fluorine cell.

King's College, Newcastle-on-Tyne. [*Received, March 2nd,* 1954.]

The Reduction of 4-Amino- and 4-Acetamido-salicylic Acids.

By A. A. Goldberg and R. S. Theobald.

[Reprint Order No. 5194.]

During a search for an easy route to 4-aminosalicylaldehyde one method presenting itself was sodium amalgam reduction of the easily accessible 4-aminosalicylic acid; Weil (*Ber.*, 1908, **41**, 4147) obtained a 60% yield of salicylaldehyde from salicylic acid by this reaction.

It was found, however, that treatment of 4-aminosalicylic acid with sodium amalgam in the presence of *p*-toluidine and boric acid effected reduction of the carboxyl and simultaneous hydrogenolysis of the amino-group; salicylidene-*p*-toluidine was the only product which could be isolated. Reduction of 4-acetamidosalicylic acid, on the other hand, yielded 4-acetamidosalicylaldehyde although in small yield.

Experimental.—Reduction of 4-aminosalicylic acid. A solution of sodium 4-aminosalicylate (20 g.) in water (650 c.c.) was stirred with sodium chloride (250 g.), finely powdered *p*-toluidine (20 g.), and boric acid (20 g.). Portionwise and alternate additions of sodium amalgam (150 g.; 4%) and boric acid (150 g.) were made during 1 hr. and the mixture stirred for a further 3 hr. This suspension was decanted from mercury, the insoluble material collected, and *p*-toluidine removed by heating it to 70° with water (1000 c.c.), cooling to 25°, and then filtering. Crystallisation of the yellow residue from alcohol (20 c.c.) gave pure salicylidene-*p*-toluidine (2·5 g.) as bright yellow needles, m. p. 92° (Found: C, 79·4; H, 6·1; N, 6·8. Calc. for $C_{14}H_{13}ON$: C, 79·7; H, 6·2; N, 6·6%). Heating the Schiff's base (2 g.) with thiosemicarbazide (2 g.) in 50% aqueous alcohol gave salicylaldehyde thiosemicarbazone (0·8 g.) which separated in almost colourless prisms, m. p. 233° (decomp.) alone and mixed with authentic material (Found: C, 48·8; H, 4·6; N, 21·3. Calc. for $C_8H_9ON_3S$: C, 49·2; H, 4·6; N, 21·5%).

Reduction of 4-acetamidosalicylic acid. A solution of 4-acetamidosalicylic acid (40 g.) and sodium carbonate (21·2 g.) in water (1 l.) and alcohol (500 c.c.) was stirred at room temperature with sodium chloride (450 g.), *p*-toluidine (40 g.), and boric acid (64 g.). Sodium amalgam (4%; 320 g.) and boric acid (320 g.) were added portionwise during 1 hr. and stirring continued for a further 4 hr. The mercury was separated, the aqueous-alcoholic suspension filtered, and the insoluble material freed from inorganic material by washing with hot water; crystallisation from alcohol gave *4-acetamido-2-hydroxybenzylidene-*p*-toluidine* (8·6 g.) in yellow needles, m. p. 212° (Found: N, 10·5. $C_{16}H_{16}O_2N_2$ requires N, 10·4%). The Schiff's base (2 g.) was refluxed with acetic anhydride (20 c.c.) for 15 min., excess of the reagent decomposed with hot water (60 c.c.), and the cooled suspension basified with aqueous ammonia. After removal of the insoluble *p*-acetotoluidide, the filtrate was acidified with acetic acid, and the precipitate of *4-acetamidosalicylaldehyde* (1 g.; m. p. 182°) collected; a sample crystallised from dilute alcohol in fine colourless needles, m. p. 184° (Found: N, 7·9. $C_9H_9O_3N$ requires N, 7·8%). The *oxime* separated from dilute alcohol in small colourless needles, m. p. 226° (decomp.) (Found: N, 14·6. $C_9H_{10}O_3N_2$ requires N, 14·4%).

A solution of the foregoing azomethine (2 g.) in boiling alcohol (100 c.c.) was mixed with a solution of thiosemicarbazide (2 g.) in water (100 c.c.); *4-acetamidosalicylaldehyde thiosemicarbazone* (1·5 g.) rapidly separated in small orange leaflets, m. p. 258—260° (decomp.) alone and on admixture with material obtained by the method of Goldberg and Walker (*J.*, 1954, 2540) (Found: N, 22·4; S, 12·8. $C_{10}H_{12}O_2N_4S$ requires N, 22·2; S, 12·7%). Hydrolysis of this (1 g.) with 2N-sodium hydroxide (50 c.c.) on the water-bath for 1 hr., followed by acidification with acetic acid, gave *4-aminosalicylaldehyde thiosemicarbazone*; this crystallised from aqueous alcohol in pale orange needles, m. p. 218—220° (Found: N, 26·6; S, 15·1. $C_8H_{10}ON_4S$ requires N, 26·7; S, 15·3%).

Ward, Blenkinsop & Co., Ltd., Research Department,
Shepton Mallet, Somerset.

[*Received, March 10th*, 1954.]

Methylation of Indoles.

By K. T. Potts and J. E. Saxton.

[Reprint Order No. 5227.]

1-Methylindoles have been of interest in our studies related to alkaloid chemistry and were not readily available. 1-Methylindole itself can be prepared from the *as*-methylphenylhydrazone of pyruvic acid (Fischer and Hess, *Ber.*, 1884, **17**, 561) or by the action of

sodamide or sodium hydride followed by methyl iodide on indole at elevated temperatures (Weissgerber, *Ber.*, 1910, **43**, 3522; Gray, *J. Amer. Chem. Soc.*, 1953, **75**, 1253). A more recent method (Shirley and Roussel, *ibid.*, p. 375) involves the treatment of indole with methyl toluene-*p*-sulphonate and anhydrous sodium carbonate in boiling xylene. The method now reported for the methylation of indole derivatives has been used in this laboratory for a number of years (see, *e.g.*, Robinson and Stephen, *Nature*, 1948, **162**, 177) and has given very satisfactory results. Originally, the *N*-sodio-derivative was prepared in liquid ammonia and then allowed to react with methyl iodide after removal of the solvent. Harman and harmine have been converted into *ind*-*N*-methylharman and *ind*-*N*-methylharmine respectively (Anet, Chakravarti, Robinson, and Schlitter, *J.*, 1954, 1242) in this manner. A logical extension of this method involved carrying out the whole reaction in liquid ammonia. The product was then isolated by means of ether after the ammonia had been allowed to evaporate. Indole, 2-methylindole, ethyl α-3-indolyl*iso*butyrate, and 3-2′-aminoethylindole (tryptamine) have been methylated in this fashion. It is interesting that the reaction can be employed in the presence of a basic amino-group; a similar type of methylation has been found to occur with phenylhydrazines (Audrieth, Weisiger, and Carter, *J. Org. Chem.*, 1941, **6**, 417).

Experimental.—1-*Methylindole*. Sodium (2·5 g.) was added in small pieces to liquid ammonia (200 c.c.) containing ferric nitrate (0·1 g.). When dissolution was complete, indole (11·7 g.) in ether (20 c.c.) was added to the stirred mixture. After 10 min., methyl iodide (16 g.) was added dropwise, and stirring was continued for a further 15 min. The ammonia was allowed to evaporate, water (50 c.c.) and ether (50 c.c.) were added, the ethereal layer was separated and dried, and the solvent removed. The crude oil ($n_D^{18\cdot5}$ 1·6078) was purified by distillation, and 1-methylindole obtained as a colourless oil, b. p. 133°/26 mm., $n_D^{18\cdot5}$ 1·6082. The yield was almost quantitative. Snyder and Eliel (*J. Amer. Chem. Soc.*, 1948, **70**, 1703) report b. p. 134—135°/31 mm. and n_D^{20} 1·6062.

The picrate was obtained from benzene as red prisms, m. p. 149—150°, alone and when mixed with a specimen prepared by the method of Fischer and Hess (*loc. cit.*).

1 : 2-*Dimethylindole*. 2-Methylindole was alkylated as above, and the product obtained as colourless plates (90%) from light petroleum (b. p. 40—60°), m. p. 56°, alone and when mixed with an authentic specimen prepared from acetone methylphenylhydrazone. The picrate was obtained from benzene as red needles, m. p. 125°, alone and when mixed with authentic 1 : 2-dimethylindole picrate (Marion and Oldfield, *Canad. J. Res.*, 1947, **25**, *B*, 1, also report m. p. 125°).

Ethyl α-(1-*methyl*-3-*indolyl*)iso*butyrate*. Ethyl α-3-indolyl*iso*butyrate (3·5 g.; Erdtman and Jonsson, *Acta Chem. Scand.*, 1954, **8**, 119) in ether (25 c.c.) was added to a stirred solution of sodamide (from 0·4 g. of sodium) in liquid ammonia (100 c.c.). Methyl iodide (2·5 g.) was then added dropwise, and the stirring continued for 30 min. The ammonia was allowed to evaporate, and the residue treated with ether (75 c.c.) and water (50 c.c.). The ethereal layer was separated, dried, and evaporated, and the residue crystallized from light petroleum (b. p. 60—80°). *Ethyl* α-(1-*methyl*-3-*indolyl*)iso*butyrate* (3·5 g.) was obtained as colourless needles, m. p. 83° (Found: C, 73·5; H, 7·55; N, 5·7. $C_{15}H_{19}O_2N$ requires C, 73·5; H, 7·75; N, 5·7%). In contrast to the starting material, this substance shows no absorption at 2·95 μ, indicating the absence of an >NH group in the molecule.

3-2′-*Aminoethyl*-1-*methylindole*. Finely powdered tryptamine (4·1 g.) was added to a solution of sodamide in liquid ammonia (from 0·6 g. of sodium in *ca.* 100 c.c. of ammonia), with efficient stirring throughout the reaction. After 5 min., methyl iodide (4·0 g.) was added carefully and the solution kept at room temperature until all the ammonia had evaporated. Water (20 c.c.) was added to the residue, the mixture extracted with ether (5 × 20 c.c.), and the ethereal layer washed with water, dried, and evaporated. Distillation of the residue gave a colourless, mobile oil (2·7 g., 60%) with a typical indole-amine odour, b. p. 112—113°/0·2 mm., n_D^{21} 1·6050 (Snyder and Eliel, *loc. cit.*, report b. p. *ca.* 108—110°/0·1 mm.) (Found: C, 75·5; H, 7·9. Calc. for $C_{11}H_{14}N_2$: C, 75·8; H, 8·1%).

The phthalimido-derivative separated as cream needles, m. p. 177°, from methanol (Manske, *Canad. J. Res.*, 1931, **5**, 597, reports m. p. 177·5°). No colour was obtained with Ehrlich's reagent even on prolonged heating.

The *picrate* separated from methanol as scarlet, rectangular plates, which lost solvent above 100° to give the yellow form, m. p. 178—179° (Found: C, 49·8; H, 4·6; N, 15·9. $C_{17}H_{17}O_7N_5,CH_3{\cdot}OH$ requires C, 49·7; H, 4·8; N, 16·1%). Snyder and Eliel (*loc. cit.*) report m. p. 178—179°. The solvated derivative shows intense absorption at 2·85 μ, showing the

presence of an OH group; a specimen dried at 100° for 6 hr. showed no absorption at this wavelength. Preparation of the picrate in acetone solution and recrystallization from the same solvent gave 1-*methyl*-N-iso*propylidenetryptamine picrate*, yellow-orange needles, m. p. 177—179°, mixed m. p. with 1-methyltryptamine picrate 160—170° (Found: C, 54·2; H, 4·8; N, 15·4. $C_{14}H_{18}N_2,C_6H_3O_7N_3$ requires C, 54·2; H, 4·8; N, 15·8%).

The authors are indebted to Professor Sir Robert Robinson, O.M., F.R.S., for his interest in this work which was carried out during the tenure of an I.C.I. Fellowship (J. E. S.).

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, March 22nd,* 1954.]

The Preparation and Freezing Point of Pure Naphthalene.

By E. F. G. HERINGTON, A. B. DENSHAM, and P. J. MALDEN.

[Reprint Order No. 5267.]

MAIR and STREIFF (*J. Res. Nat. Bur. Stand.*, 1940, **24**, 395) have described the preparation, by crystallization from ethyl alcohol and by distillation, of a sample of naphthalene of purity 99·94 ± 0·04 moles % and freezing point 80·24°. These workers estimated the freezing point of the 100% pure material as 80·27° ± 0·02°. Mathieu (*Mém. Acad. roy. Belg.*, 1953, **28**, No. 2) prepared a sample of naphthalene of $99{\cdot}99_1$ ± 0·002 moles % purity by fractional crystallization from alcohol and acetone, followed by simple distillation and recrystallization from the liquid melt. The freezing points of the sample and of the 100% pure material were recorded as 80·279° and 80·284° ± 0·003° respectively.

The present note describes the preparation of a sample of naphthalene of low sulphur content and 99·978 ± 0·10 moles % purity. The freezing point of the actual sample and of the 100% pure material were shown to be 80·287° ± 0·002° and 80·300° ± 0·006° respectively. This figure for the freezing point of the 100% pure material is in agreement with the values given above when consideration is given to the standard deviations of the various measurements. However, since the freezing point of our actual specimen (*viz.*, 80·287° ± 0·002°) is higher than that ascribed to the 100% pure material by Mathieu (80·284° ± 0·003°) the latter is probably a little low. The best value for the freezing point of 100% pure naphthalene, *viz.*, 80·287° ± 0·003° is obtained by combining Mathieu's and our value into a grand mean and weighting the individual measurements by the squares of the reciprocals of their standard deviations in the usual manner.

Experimental.—Preparation. Thionaphthen, first isolated from a coal tar fraction by reaction with sodamide (Weissberger and Krüber, *Ber.*, 1920, **53**, 1551), is the main impurity in commercially pure crystal naphthalene (Armstrong, Densham, and Gough, *J.*, 1950, 3359). Preliminary experiments showed that recrystallization and simple distillation did not remove this sulphur compound very effectively: for example, crystal naphthalene, after two recrystallizations from methanol and fractionation, still had a sulphur content of 0·08% by weight. The following procedure was therefore adopted.

Commercial crystal naphthalene was kept overnight at 140° under a stream of nitrogen in order to remove water, and the product was then stirred at 140° for a further 24 hr. with 5% of sodamide powder. The naphthalene was decanted and was then stirred at 180° with 1% of sodamide for a further 24 hr. The melt was filtered through glass wool and was fractionated in an adiabatic column, packed with glass helices, of 10 theoretical-plate efficiency. The middle fraction was twice recrystallized from redistilled methanol and redistilled. The distillate after solidification was broken up in an agate mortar. The sulphur content, determined by Grote-Krekeler's quartz-tube method (*Angew. Chem.*, 1933, **46**, 106), was less than 0·002% by weight.

Purity and freezing-point determinations. The purity and the f. p. of the sample were measured by means of the apparatus described by Herington and Handley (*J.*, 1950, 199). Further details of this technique and of the calculations have been given recently (Biddiscombe, Coulson, Handley, and Herington, *J.*, 1954, 1957). This method of analysis of the f. p. curves necessitates the addition of known amounts of impurity and for this purpose anthracene was chosen because Mathews (*J. Amer. Chem. Soc.*, 1917, **39**, 1125) has established that anthracene produces the theoretical cryoscopic depression when dissolved in naphthalene. The anthracene employed in the present experiments was a synthetic specimen of high purity.

We express our thanks to Mr. R. Handley and Mr. D. Harrop for assistance with the freezing-point measurements. We also thank the Director of the Chemical Research Laboratory and the North Thames Gas Board for permission to publish this paper.

CHEMICAL RESEARCH LABORATORY, TEDDINGTON, MIDDLESEX.
FULHAM LABORATORY, NORTH THAMES GAS BOARD,
KING'S ROAD, LONDON, S.W.6. [*Received, March* 31*st*, 1954.]

Methyl 3β-*Iodochol-5-enate.*

By W. KLYNE.

[Reprint Order No. 5278.]

METHYL 3β-IODOCHOL-5-ENATE has been prepared from the corresponding 3β-hydroxy-ester by the method used by Beynon, Heilbron, and Spring (*J.*, 1936, 737) in the cholesterol series. The toluene-*p*-sulphonate of methyl 3β-hydroxychol-5-enate was treated with potassium acetate in methanol to give the 6β-methoxy-3 : 5-*cyclo*-compound, which with hydriodic acid in acetic acid yielded methyl 3β-iodochol-5-enate. The β-configuration of the iodine atom is allotted by analogy with that for cholesteryl iodide (Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64). Molecular-rotation differences in the cholenic ester series show satisfactory agreement with those in the cholesterol series (cf. Barton and Brooks, *J.*, 1949, 2596).

Experimental.—M. p.'s are corrected. Optical rotations were determined in $CHCl_3$ at 20—25° (*c*, 1—2%). The " usual working up " followed Barton and Brooks, *J.*, 1951, 257, except that ethereal solutions of products were dried with Na_2SO_4 before distillation. Light petroleum was the fraction of b. p. 60—80°.

Methyl 3β-*toluene*-p-*sulphonyloxychol-5-enate.* This *ester* was obtained by treating the hydroxy-ester (m. p. 141—143°) with toluene-*p*-sulphonyl chloride in pyridine, and crystallised from light petroleum, containing a little ethyl acetate or chloroform, as rosettes of stout prisms, m. p. 121—123°, $[\alpha]_D$ −40°, $[M]_D$ −215° (Found : C, 70·7; H, 8·5; S, 6·3. $C_{32}H_{46}O_5S$ requires C, 70·8; H, 8·5; S, 5·9%).

Methyl 6β-*methoxy*-3 : 5-cyclo*cholanate.* The above ester (3·8 g.) and anhydrous potassium acetate (5·0 g.) were refluxed in methanol (200 ml.) for 2 hr. The usual working up yielded a gum (2·6 g.), which crystallised on long standing. The cyclo-*compound* after two recrystallisations from methanol had m. p. 62—65° (decomp.), $[\alpha]_D$ +43°, $[M]_D$ +173° (Found : C, 77·3; H, 10·2. $C_{26}H_{42}O_3$ requires C, 77·6; H, 10·5%).

Methyl 3β-*iodochol-5-enate.* The *cyclo*-compound (1·27 g.) was allowed to stand overnight with glacial acetic acid (100 ml.) and aqueous hydriodic acid (*d* 1·7; 12 ml.). Addition of aqueous sodium sulphite (100 ml.; 10%) precipitated the crude product which was chromatographed on alumina; light petroleum–benzene (4 : 1 v/v) eluted a white solid which crystallised from light petroleum. The *iodo*-compound formed large prisms (420 mg.), m. p. 110—112° (the supercooled liquid showed a striking bluish-violet or bluish-green fluorescence), $[\alpha]_D$ −15°, $[M]_D$ −75° (Found : C, 60·3; H, 8·1; I, 25·1. $C_{25}H_{39}O_2I$ requires C, 60·2; H, 7·9; I, 25·5%).

I am greatly indebted to N. V. Organon, Oss, Netherlands, for a generous gift of methyl 3β-hydroxychol-5-enate.

POSTGRADUATE MEDICAL SCHOOL, LONDON, W.12. [*Received, April* 3*rd*, 1954.]

The Structure of the Oxazoline Derivatives of Glucose and Galactose.

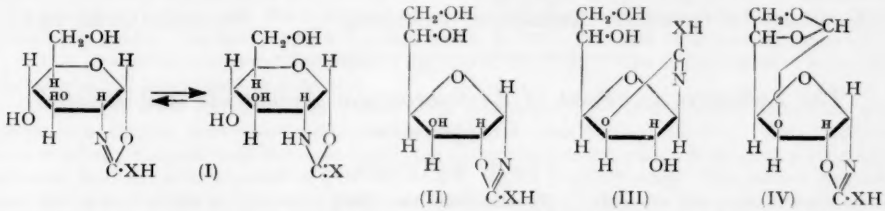
By J. C. P. SCHWARZ.

[Reprint Order No. 5280.]

ZEMPLÉN, GERECS, and RADOS (*Ber.*, 1936, **69**, 748) obtained a compound from the reaction of D-glucose with potassium thiocyanate, to which they gave the name " μ-thiolglucoxazoline " and the structure (I; X = S). Oxidation with hydrogen peroxide in alkaline solution converted this compound into μ-hydroxyglucoxazoline, which was given the structure (I; X = O). Similar structures have also been suggested for the compounds obtained by the action of thiocyanic acid on D-fructose (Zemplén, Gerecs, and Illés, *Ber.*, 1938, **71**, 590), D-galactose, D-xylose, and L-arabinose (Bromund and Herbst, *J. Org. Chem.*, 1945, **10**, 267).

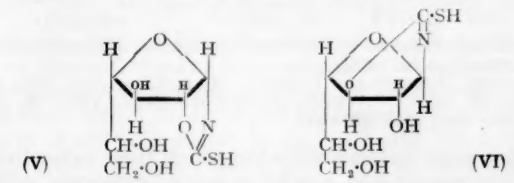
More recently Edward and Martlew (*Chem. and Ind.*, 1952, 1034) hydrolysed μ-thiolglucoxazoline with concentrated hydrochloric acid. Using paper chromatography they were able to demonstrate the presence of 1-aminoglucose and diglucosylamine in the products, but no glucosamine could be detected. This suggests that the nitrogen atom in the above oxazolines is attached to $C_{(1)}$ and not to $C_{(2)}$.

μ-Hydroxyglucoxazoline has now been oxidised with sodium periodate. It consumed 1 mol. of periodate with production of 0·94 mol. of formaldehyde and no formic acid. μ-Thiolglucoxazoline gave 0·7 mol. of formaldehyde. These results are consistent only with the furanose structures (II and III; X = S or O) and their tautomers. μ-Thiolglucoxazoline readily gave an orthoformate when shaken with ethyl orthoformate in methanol in the presence of a little hydrogen chloride. This derivative has the structure (IV; X = S) as the formation of an orthoformate from (III; X = S) is sterically impossible. The glucoxazolines therefore have the structure (II; X = S or O). Oxidation with hydrogen peroxide converted the orthoformate (IV; X = S) into its oxygen analogue (IV; X = O).



μ-Thiolgalactoxazoline (Bromund and Herbst, *loc. cit.*) also gave formaldehyde (0·6 mol.) on oxidation with sodium periodate. By analogy with the glucose compounds, the structure (V) seems more probable than (VI). An attempt to verify this by methylation was abandoned, as the compound was sensitive to alkali and practically insoluble in non-polar solvents.

The reaction of μ-thiolglucoxazoline and μ-thiolgalactoxazoline with sodium periodate is complicated by the oxidation of the sulphur atom. In both cases iodine was liberated and the formation of sulphate could be demonstrated. During the oxidation of the μ-thiolglucoxazoline the solution became cloudy (sulphur?); this also occurred at higher concentrations in the oxidation of μ-thiolgalactoxazoline. The production of iodine is probably due to the reduction of iodate by the thioloxazolines. Titration with sodium thiosulphate after the addition of potassium iodide and sulphuric acid showed that about 9·6 equivs. of oxidising agent (periodate and iodate) had been consumed by the thioloxazolines. Theoretically 10 equivs. of oxidant are required to oxidise the thioloxazolines to the hydroxyoxazolines and sulphuric acid, and to bring about one glycol fission.



Experimental.—Periodate oxidations were carried out in the dark with unbuffered sodium periodate (0·05—0·2M). Formaldehyde was estimated by Bell's method (*J.*, 1948, 994). However no phosphate buffer was added and, with the thioloxazolines, a slightly larger quantity of periodate was used.

μ-Hydroxyglucoxazoline. Periodate consumption (arsenite method): 0·99 (5 min.), 0·99 mol. (75 min.). Formaldehyde: 0·94 mol. (25 min.).

μ-Thiolglucoxazoline. Oxidant consumption (periodate and iodate): 9·6 equivs. (10 and 50 min.). Formaldehyde: 0·7 mol. (25 min.).

μ-Thiolgalactoxazoline. Oxidant consumption: 9·6 (15 min.), 9·8 equivs. (40 min.). Formaldehyde: 0·6 mol. (30 min.).

μ-Thiolglucoxazoline orthoformate. Finely powdered μ-thiolglucoxazoline (2 g.) was shaken

for 2 hr. with ethyl orthoformate (2·6 c.c.), dry methanol (2 c.c.), and 20% methanolic hydrogen chloride (0·13 c.c.). After filtration the solid product was washed, first, with a little methanol, then with much water. The *orthoformate* (1·9 g.) crystallised from much ethyl acetate as colourless needles, m. p. 255° (decomp.), $[\alpha]_D^{21}$ +20° (*c*, 1·96 in 0·1N-NaOH) (Found: C, 41·9; H, 3·3; S, 13·7. $C_8H_9O_5SN$ requires C, 41·6; H, 3·9; S, 13·9%), and dissolved in cold dilute aqueous sodium hydroxide whence it was recovered on acidification.

μ-Hydroxyglucoxazoline orthoformate. Hydrogen peroxide (100-vol.; 30 c.c.) was added in small portions to μ-thiolglucoxazoline orthoformate (7·3 g.) in 1·05N-sodium hydroxide (70 c.c.) at 25—30° (cooling). After 30 min., the mixture was cooled in the refrigerator and the crude product [m. p. 215—220° (decomp.); 5·7 g.] was filtered off. The *orthoformate* crystallised from ethanol containing a little water as needles, m. p. 220—225° (decomp.), $[\alpha]_D^{19}$ +32° (*c*, 0·396 in H_2O) (Found: C, 44·6; H, 4·2. $C_9H_9O_6N$ requires C, 44·7; H, 4·2%).

The author is grateful to Professor E. L. Hirst, F.R.S., for advice and encouragement, and to the University of Edinburgh for the award of an Imperial Chemical Industries Research Fellowship.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, April 5th*, 1954.]

The Dielectric Constant of Trifluoroacetic Anhydride and Related Compounds.

By J. M. TEDDER.

[Reprint Order No. 5281.]

THE dielectric constant of trifluoroacetic anhydride is of interest, since it has been suggested that certain reactions occurring in this medium are of an ionic character (Bourne, Randles, Tatlow, and Tedder, *Nature*, 1951, **168**, 942; Bourne, Randles, Stacey, Tatlow, and Tedder, *J. Amer. Chem. Soc.*, in the press). The value obtained ($\varepsilon = 2{\cdot}7$ at 25°) is considerably lower than that for trifluoroacetic acid ($\varepsilon = 8{\cdot}2$ at 25°), in sharp contrast to their hydrocarbon analogues where the dielectric constant of acetic anhydride ($\varepsilon = 21$ at 25°) is very much higher than that of acetic acid ($\varepsilon = 6{\cdot}3$ at 25°). The dielectric constants of dichloro- and trichloro-acetic anhydrides have also been measured for comparison and the values obtained for the complete series are tabulated below.

	Anhydride		Acid	
	Conductivity ($\kappa \times 10^7$, mhos)	Dielectric constant ε	Conductivity ($\kappa \times 10^7$, mhos)	Dielectric constant ε
$CF_3{\cdot}CO-$	<0·001 (25°) [a]	2·7 (25°) [a]	3·5 (25°) [a]	8·2 (25°) [a]
$CCl_3{\cdot}CO-$	0·002 (25°) [a]	5·0 (25°) [a]	0·06 (60°) [c]	4·5 (60°) [d]
$CHCl_2{\cdot}CO-$	0·4 (25°) [a] *	15·8 (25°) [a] *	—	7·8 (60°) [d]
$CH_2Cl{\cdot}CO-$	—	—	14 (60°) [c]	20 (60°) [d]
$CH_3{\cdot}CO-$	3·4 (25°) [a] *	21 (25°) [a] *	0·06 (25°) [e]	6·2 (30°) [b]

* These readings of high dielectric constant and appreciable conductivity should be regarded as approximations rather than precise values.

[a] Present investigation. [b] Smyth and Rogers, *J. Amer. Chem. Soc.*, 1930, **52**, 1824. [c] Kendall and Gross, *ibid.*, 1921, **43**, 1426. [d] Walden, *Z. physikal. Chem.*, 1910, **70**, 569. [e] Kolthoff and Willman, *J. Amer. Chem. Soc.*, 1934, **56**, 1007.

There are clearly too many factors involved to permit these values to be analysed. The value obtained for trifluoroacetic acid, $\varepsilon = 8{\cdot}2$, is in good agreement with that reported by Dannhauser and Cole (*J. Amer. Chem. Soc.*, 1952, **74**, 6105) and confirms their value rather than the earlier one of Simons and Lorentzen (*ibid.*, 1950, **72**, 1426). An attempt was also made to measure the dielectric constant of mixtures of acetic anhydride and trifluoroacetic anhydride. Previous work (Randles, Tatlow, and Tedder, *J.*, 1954, 436) has shown that a conductivity maximum occurs for this system when the mole fraction of trifluoroacetic anhydride is about 0·25. In the present investigation it was found that the equilibrium between the two anhydrides is set up slowly, and apparently a chemical reaction (possibly the attack of acetic anhydride by $CH_3{\cdot}CO^+$) also occurs (cf. Randles, Tatlow, and Tedder, *loc. cit.*). These difficulties, coupled with relatively high conductivities (no reasonable balance could be obtained for conductivities greater than 2×10^{-6} mhos with the bridge

circuit used), made precise readings impossible. It appeared, however, that there is probably a dielectric-constant maximum as well as conductivity maximum for this system.

Experimental.—The cell and capacitance bridge. The cell, a simplified model of that described by Smyth and Morgan (*J. Amer. Chem. Soc.*, 1928, **50**, 1547), had been designed and previously used by Verhoek and Smith (unpublished work). Capacitance measurements were made with a General Radio Company Type 716-C Capacitance Bridge (substitution method) and a Type 539-B variable condenser as balancing capacitor, and an oscillograph was used as detector. The bridge was most sensitive at 10^5 cycles and the readings reported were made at this frequency. The cell was immersed in an oil-bath maintained at approx. 25°; very rigid temperature control was not attempted. The cell was standardized with carefully redistilled C.P. benzene which was assumed to have a dielectric constant of 2·274 at 25°.

Materials. Trifluoroacetic acid and trifluoroacetic anhydride were prepared as previously described (Randles, Tatlow, and Tedder, *loc. cit.*). Commercial acetic anhydride (Eastman Kodak 99—100%) was purified by fractionation and the centre fraction, b. p. 137—137·5°, was used. Trichloro- and dichloro-acetic anhydride were prepared by distilling the commercial acids over phosphoric oxide, and the crude anhydrides so obtained were then redistilled over fresh phosphoric oxide. Trichloroacetic anhydride had b. p. 220—222° and dichloroacetic anhydride b. p. 210° (the latter compound decomposed slightly at the b. p.). The distillates were tested for phosphorus but none could be detected.

Mixtures of acetic anhydride and trifluoroacetic anhydride. Redistilled acetic anhydride was placed in a receiver, into which trifluoroacetic anhydride was distilled directly. Two mixtures were studied; the first, with the mole fraction of trifluoroacetic anhydride 0·82, gave reasonably constant readings over a period of 2 hr. ($\varepsilon_{23} = 4{\cdot}4$; $\kappa_{23} \approx 1 \times 10^{-8}$ mho). The second mixture with the mole fraction of trifluoroacetic anhydride 0·26, gave values for the dielectric constant and conductivity which increased with time. When the mixture was first added to the cell the values obtained were $\varepsilon_{25} \approx 20$; $\kappa_{25} \approx 6{\cdot}2 \times 10^{-7}$ mho, but after 2 hr. the dielectric constant had risen somewhat ($\varepsilon_{25} \approx 29$) and the conductivity had greatly increased ($\kappa_{25} \approx 1{\cdot}3 \times 10^{-6}$ mho). After 24 hr. the conductivity had risen to such an extent that it was no longer possible to balance the bridge, and some chemical process had taken place causing the mixture to darken.

The author is very grateful to Professor A. L. Henne for his encouragement and interest, and to Professor F. Verhoek for his advice and criticism.

CHEMISTRY DEPARTMENT, THE OHIO STATE UNIVERSITY,
COLUMBUS 10, OHIO, U.S.A.
[Present address: CHEMISTRY DEPARTMENT,
THE UNIVERSITY, EDINBURGH, 9.]

[*Received, April 5th*, 1954.]

The Cryoscopic Behaviour of Non-electrolytes in Sulphuric Acid.

By P. A. H. WYATT.

[Reprint Order No. 5284.]

THE author recently (*J.*, 1953, 1175) drew attention to one source of complication in cryoscopic studies on dissociating solvents, showing that the influence of dissociation heat effects upon the cryoscopic constant (k_f) could be large in the case of a solvent of appreciable dissociation such as nitric acid. An attempt was also made to invoke a thermal effect to explain the behaviour of nitro-compounds in sulphuric acid, but further consideration of Kunzler and Giauque's data (*J. Amer. Chem. Soc.*, 1952, **74**, 3472) shows this explanation to be unlikely. In fact, their Fig. 2 indicates that sulphuric acid is a normal dissociating solvent, with normal partial heat content values corresponding to a heat of dissociation of *ca.* 8 kcal. per mole of H_2O involved in the dissociation reaction. Whatever the form of dissociation, it follows that k_f for sulphuric acid will only vary from 6·12 deg. mole^{-1} kg. in the second place of decimals.

The object of the present Note is to draw attention to another source of complication which has been overlooked in this connexion, namely, the phenomenon of "salting-out." Although well investigated in aqueous systems (see Long and McDevit, *Chem. Reviews*, 1952, **51**, 119), this effect has been somewhat neglected for other solvents. The following observations combine to make a strong case for its importance in the solvent sulphuric acid.

(1) The solute 2 : 4 : 6-trinitrotoluene gives a greater depression of freezing point in

sulphuric acid containing a little water than would be expected for a non-electrolyte from $k_f = 6{\cdot}12$ (Gillespie, *J.*, 1950, 2544; Wyatt, *loc. cit.*).

(2) Spectrophotometric evidence shows that this nitro-compound is un-ionized in 100% sulphuric acid (Brand, Horning, and Thornley, *J.*, 1952, 1374).

(3) The addition of water reduces the solubility of polynitro-compounds in concentrated sulphuric acid.

(4) For water as solvent, " the depression of the freezing point produced by a salt and a non-electrolyte together is greater than the sum of the depressions produced by each singly " (Butler, " Chemical Thermodynamics," Macmillan, London, 4th Ed., 1946, p. 465).

(5) The high dielectric constant of sulphuric acid may reasonably be expected to lead to important local distribution effects amongst solutes of lower polarity.

(6) Whether salt effects are to be related to molar fractions or to volume concentrations, similar effects to those in water might be expected to occur in sulphuric acid at considerably lower molalities, because of the larger molecular weight and density of the solvent.

(7) Other polynitro-compounds in sulphuric acid behave cryoscopically in the same way as trinitrotoluene, giving molal depressions $>6{\cdot}12$ in the presence of a little water and $<6{\cdot}12$ in the presence of excess of sulphuric anhydride *or of potassium hydrogen sulphate* (Brayford and Wyatt, to be published). The latter observation is important since (i) it is inconsistent with Gillespie's weak-base hypothesis, and (ii) it suggests the possibility that in this solvent salts having activity coefficients less than 1 (H_3O,HSO_4) may salt out nitro-compounds (analogous to the common behaviour of salts in water), whilst salts with activity coefficients greater than 1 ($KHSO_4$) may salt them in (at least for small concentrations of non-electrolyte). Experience with water as solvent does not suggest that all non-electrolytes will behave in the same way, and the behaviour of sulphuryl chloride and chlorosulphonic acid in sulphuric acid (Gillespie, Hughes, and Ingold, *J.*, 1950, 2473) compared with that of the nitro-compounds, may illustrate the variability to be found in this solvent.

It follows from this argument that the design of the standard cryoscopic experiments with sulphuric acid, in which bisulphates are added to suppress solvent dissociation, is not well suited to deciding whether a given solute is a non-electrolyte or not, since the conditions employed are such as to invite complications from salting-out and salting-in. (This type of problem is better solved unambiguously by the spectrophotometric method.) If this assessment of the importance of variations in the activity coefficients of non-electrolytes is correct, it will be of interest in the application of Brønsted's theory of kinetic activity factors to reactions such as nitration and sulphonation in concentrated sulphuric acid.

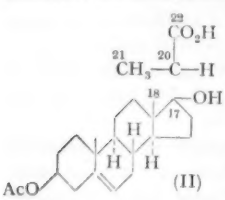
THE UNIVERSITY, SHEFFIELD. [*Received, April 6th,* 1954.]

The Steroid Series. Part III. Alteration to Nomenclature.

By D. H. HEY, JOHN HONEYMAN, and W. J. PEAL.

[Reprint Order No. 5286.]

THE names of a number of compounds in our paper " The Steroid Series, Part III " (*J.*, 1954, 185) are not in accordance with the accepted rule for naming steroid acids and their derivatives. For example, the compound illustrated, and identified as (II) in our original paper, was incorrectly named as a derivative of pregnan-20-oic acid. The nomenclature of these compounds should be based on their relationship to bisnorcholanic acid. In this way, (II) is 3β-acetoxy-17β-hydroxy-20β-bisnorchol-5-enic acid. The adoption of this method of nomenclature necessitates the following revised names :



(II)

(*a*) 3-acetoxy-17-hydroxy-20(α or β)-bisnorchol-5-enic acids and esters for 3-acetoxy-17-hydroxy-20(α or β)-pregn-5-en-20-oic acids and esters;

(*b*) 3-acetoxy-20(α or β)-bisnorchola-5 : 16-dienic acids and esters for 3-acetoxy-20(α or β)-pregna-5 : 16-dien-20-oic acids and esters;

(*c*) 3β-acetoxybisnorchola-5 : 17(20)-dienic acid for 3β-acetoxypregna-5 : 17(20)-dien-20-oic acid;

(*d*) 20β-bisnorchola-5 : 16-diene-3β : 22-diol diacetate for 20β-pregna-5 : 16-diene-3β : 22-diol diacetate; and

(*e*) 20β-bisnorchol-5-ene-3β : 17β : 22-triol 3 : 22-diacetate for 20β-pregn-5-ene-3β : 17β : 22-triol 3 : 22-diacetate.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, March 29th*, 1954.]

Synthetic Œstrogens.

By J. GRUNDY.

[Reprint Order No. 5325.]

SINCE work cannot be continued, the preliminary chemical results of an attempt to modify the Schueler hypothesis of œstrogenic activity (*Science*, 1946, **103**, 221) are now reported.

The series of compounds (I)—(VI) was synthesised; these contain two functional groups, at various spacings, capable of reacting *in vivo* with amino-groups. The alkoxycarbonylamino-group in (I)—(IV) was included on the basis of a suggestion in connection with cytotoxic action (Rose, Hendrey, and Walpole, *Nature*, 1950, **165**, 993); compounds (V) and (VI) contain the related alkoxycarbonyloxy-group. Biological tests have not been carried out.

(I) *p*-$MeO_2C{\cdot}NH{\cdot}C_6H_4{\cdot}NH{\cdot}CO_2Me$

(II) *p*-$EtO_2C{\cdot}NH{\cdot}C_6H_4{\cdot}NH{\cdot}CO_2Et$

(III) *p*-$EtO_2C{\cdot}NH{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CO_2H$

(IV) *p*-$MeO_2C{\cdot}NH{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CO_2H$

(V) *p*-$MeO_2C{\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}CO_2Me$

(VI) *p*-$EtO_2C{\cdot}O{\cdot}C_6H_4{\cdot}O{\cdot}CO_2Et$

p-Nitrophenoxyacetic acid has been prepared in 50% yield by the sodium chloroacetate method (Minton and Stephen, *J.*, 1922, **121**, 1591). It can, however, be obtained in 96% yield by the action of ethyl chloroacetate on sodium *p*-nitrophenoxide in triethylene glycol at 180—200°. The nitro-acid is most satisfactorily reduced by ferrous sulphate–ammonia (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 1435).

Experimental.—**1 : 4-*Dimethoxy- and* 1 : 4-*diethoxy-carbonyloxybenzene*.** These were produced by the action of the alkyl chloroformate (0·06 mole) on quinol (0·02 mole) in 20% sodium hydroxide. The products were recrystallised from alcohol. The dimethoxy-compound formed plates (0·019 mole), m. p. 113—114° (Found: C, 54·1; H, 4·6. Calc. for $C_{10}H_{10}O_6$: C, 53·2; H, 4·4%); the diethoxy-compound white needles (0·019 mole), m. p. 100—101° (Found: C, 56·8; H, 5·4. Calc. for $C_{12}H_{14}O_6$: C, 56·7; H, 5·5%).

1 : 4-*Dimethoxy- and* 1 : 4-*diethoxy-carbonylaminobenzene*. Acylation of *p*-phenylenediamine (0·02 mole) in acetic acid–sodium acetate solution with the alkyl chloroformate (0·06 mole) gave the *dimethoxy*-compound as white needles (0·018 mole), m. p. 210—211° (Found: N, 12·4. $C_{10}H_{12}O_4N_2$ requires N, 12·5%), and the diethoxy-compound (also white needles) (0·019 mole), m. p. 195—196° (Found: N, 11·1. Calc. for $C_{12}H_{16}O_4N_2$: N, 11·1%).

p-*Aminophenoxyacetic acid*. Sodium *p*-nitrophenoxide (32·2 g.) in triethylene glycol (40 ml.) was heated to 120°, ethyl chloroacetate (20·9 ml.) was added, and the temperature was raised to 180—200°. Reaction was complete after 1 hr., and the cooled mixture was then poured into excess of 10% sulphuric acid. The mixture was refluxed until homogeneous, and on cooling, pale yellow plates (37·8 g.) of *p*-nitrophenoxyacetic acid, m. p. 187—188° (Found: N, 7·1. Calc. for $C_8H_7O_5N$: N, 7·7%), were obtained. This acid (20 g.) when reduced with ferrous sulphate–ammonia gave white needles (10 g.), m. p. 250° (decomp.), of the amino-acid (Found: N, 8·8. Calc. for $C_8H_9O_3N$: N, 8·9%).

p-*Methoxy- and* p-*ethoxy-carbonylaminophenoxyacetic acid*. To *p*-aminophenoxyacetic acid (3 g.) in 10% sodium hydrogen carbonate solution (30 ml.) was added in portions, with stirring, a slight excess of the alkyl chloroformate. The cold mixture was acidified with dilute hydrochloric acid, and the coloured solids obtained were treated with charcoal in hot water. The p-*methoxy*-compound formed white plates (4 g.), m. p. 164—165° (Found: C, 53·5; H, 5·1; N, 6·7. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2%); the p-*ethoxy*-compound white needles (4 g.), m. p. 144—145° (Found: C, 55·4; H, 5·5; N, 6·25. $C_{11}H_{13}O_5N$ requires C, 55·2; H, 5·4; N, 5·9%).

THE TECHNICAL COLLEGE, BLACKBURN. [*Received, April 22nd*, 1954.]

Some Applications of the Separation of Large Molecules and Colloidal Particles.

CENTENARY LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY IN LONDON ON NOVEMBER 19TH, 1953.

By ARNE TISELIUS.

To the chemist the word separation is closely associated with preparative and analytical work but there is no doubt that all of us realize that separation methods form the key to some of the greatest problems in chemistry. It is significant that the Dutch word Scheikunde—the art of separation—still means chemistry as a whole, and we have many recent examples which demonstrate how the development of new and highly specific methods of separation have opened new fields to the structural chemist. I have chosen as the subject for this lecture a field in which such methods have made great contributions to our knowledge and where, as I see it, the future holds great promise. I shall not at all limit myself to work done in my own laboratory; I shall rather try to emphasize some general aspects of the development in this highly fruitful field, particularly in biochemistry, and I shall briefly touch on some possible unexplored applications.

When discussing the methods of colloid separation it is to be remembered that some of the most valuable and interesting applications of such methods have been made with substances which barely or not at all deserve to be called colloids. Such has been the case, for example, in the extension of electrophoresis from proteins to peptides and amino-acids. Despite the title of my lecture it is very tempting to include some of this work here.

A suitable classification of colloid separation methods would be to distinguish between procedures where the material remains in one phase during the separation, and operations depending upon the transfer from one phase to another. In the first case (*e.g.*, ultra-centrifugation, electrophoresis, diffusion, thermodiffusion, ultra-filtration) differences in rates of migration through a medium are utilized; in the second, other effects come into play (salting out, partition). We have, with this classification, to let the " surface " separation methods (adsorption, flotation, adsorption chromatography) form an intermediate group, characterized by the separation occurring at the interface between phases. This classification has significance also from another point of view, especially when dealing with biocolloids, which often suffer irreversible changes if they have to be transferred from one phase to another.

Now it is not at all my intention to describe these methods one after another, but rather to point towards some recent developments and their applications.

It is interesting to note how the chemical nature of colloidal particles often played a subordinate role in the early development of colloid chemistry. The classical investigations on Brownian movement and sedimentation were made on systems with particles sometimes of gold, sometimes of mastic, or other even less-defined material. In such cases this was, of course, justified as interest lay exclusively in certain physical properties which depend only on particle size, but there are many other cases, particularly in the application of colloid chemistry to biological phenomena, where too exclusively physical considerations have led to schematic and over-simplified theories. If, thus, chemical specificity was neglected by the early colloid chemistry it is today predominant, and particularly so with biocolloids. This development is also reflected in the frequent use of the term " macromolecules " instead of " particles " in investigations dealing with an important group of substances in this field.

On the other hand, in colloid chemistry the methods of separation are mostly based on physical phenomena, and this to such an extent that they are also utilized for determination of important physical characteristics of colloid substances such as particle size, shape, and surface electric potential. Also it should be remembered that physical methods, being usually more gentle than those based on chemical reactions, have great advantages when we have to deal with substances which easily undergo irreversible changes (*e.g.*, many biocolloids).

The applications of the methods to which I shall refer thus have a dual purpose: the separation, and the measurement of a physical property on which the separation depends. Thus, in ultra-centrifugation and electrophoresis the rate of sedimentation or the electrophoretic mobility can be measured in the same apparatus, and often even in the same experiment, in which the separation of a complex system into its components is studied. There is, however,

a natural tendency towards differentiation in this respect and the construction of separation apparatus is now often modified according to whether quantitative characterization or merely separation is the chief object. It should be noted, however, that with colloids and macromolecules the quantitative characterization possible by such methods is often among the best means of identification. Thus, even if preparative separation is the chief purpose it may be desirable not to loose entirely the possibility of quantitative characterization (by rates of sedimentation or migration) just as a fractional distillation and crystallization should, if possible, be carried out so that the boiling points and solubilities of the components are under continuous control.

One of the most important developments in colloid separation during recent years is the construction of high-speed ultra-centrifuges of large capacity, for purposes of separation. There are commercially available machines with rotors taking up to 1100 ml. at 20,000 r.p.m. (42,000 g) or 162 ml. at 40,000 r.p.m. (105,000 g) which have found extensive use in biochemical and virus laboratories, and thus have facilitated, among other things, also investigation of the nature of submicroscopic particular matter other than virus, occurring in biological material. The isolation of materials such as mitochondria, microsomes, and similar particles of electron-microscopic dimensions in quantity has permitted investigation of their chemical nature and particularly their enzymic function. This is an extremely interesting field and I shall return to these problems later.

The extension of methods of separating colloids to crystalloid substances which are in the molecular-weight region of, let us say, 1000—10,000 appears to be particularly important and fruitful, especially as there is a lack of methods for dealing with substances of this range. Thus it is of great value that molecular-weight determinations can now be made even in this range by ultra-centrifugal methods, thereby avoiding some of the difficulties due to impurities which disturb such determinations by other procedures (freezing point, vapour pressure, osmotic pressure). This development is largely due to the method of interpreting sedimentation diagrams developed by Archibald, and now used as routine in several laboratories. It makes it possible to evaluate sedimentation diagrams in which the boundary does not leave the meniscus in the ultra-centrifuge cell completely, owing to sedimentation being too slow and diffusion too fast.[1]

In this way Pedersen and his colleagues [2] in Uppsala obtained good values for the molecular weight even of sucrose (*M*, 342), and the procedure has been very useful in determining molecular weights of polypeptides. As an example I may mention that Porath in my laboratory determined the molecular weight of the antibiotically active polypeptide bacitracin as 1460, in good agreement with the minimum (1496) calculated from the sulphur content and also with the value found by Craig who used a method based on the influence of substitution on partition coefficients.

The same problem has recently been attacked in a somewhat different way by Kegeles [3] and by Pickels, Harrington, and Schachman [4] by arranging a boundary starting in the middle of the cell (a so-called synthetic boundary) instead of letting it be formed spontaneously at the top as usual. In this way even a very slowly moving boundary will migrate sufficiently before it is too much blurred by diffusion, to make it possible to determine directly the rate of sedimentation. Thus these authors have studied the sedimentation of, *e.g.*, dextrins, salmine, clupein, and vitamin B_{12}. No doubt recent developments of diffusion methods employing interferometric observation will also be useful in this field.

Returning now to the colloids and macromolecules proper, it is to be noted that ultra-centrifugation—whether it is made for particle-size or molecular-weight determinations or for separations—is almost always performed as a " boundary " separation. This means that the separation is never complete: the centrifuge cell contains a number of partially overlapping layers of the different components. This corresponds to what is also the usual procedure in electrophoresis and in the so-called frontal analysis in chromatography. If the rates of sedimentation are sufficiently different such experiments may be utilized for complete separation of substances (the " up-and-down centrifugation " used in virus purification), but with smaller

[1] W. J. Archibald, *J. Phys. Colloid Chem.*, 1947, **51**, 1204; see also D. F. Waugh and D. A. Yphantis, *J. Phys. Chem.*, 1953, **57**, 312.
[2] C. H. Li, A. Tiselius, K. O. Pedersen, L. Hagdahl, and H. Carstensen, *J. Biol. Chem.*, 1951, **190**, 326.
[3] G. Kegeles, *J. Amer. Chem. Soc.*, 1952, **74**, 5532.
[4] E. G. Pickels, W. F. Harrington, and H. K. Schachman, *Proc. Nat. Acad. Sci.*, 1952, **38**, 943; see also H. K. Schachman and W. F. Harrington (*J. Polymer Sci.*, 1954, **12**, 379).

differences this results in incomplete separation unless the experiment is repeated many times. It would be highly desirable to be able to perform " zone " separations in the ultra-centrifuge, that is, to obtain the fractions completely separated in layers, in analogy with chromatography or zone electrophoresis. Obviously the technical obstacle to be overcome is the stabilization of the zones and this is no doubt a difficult problem, especially if one wants to be able to remove the separated fractions from the cell. Use of density gradients to stabilize such " zone sedimentation " has been attempted, for example, by Brakke [5] who has separated virus preparations into zones in an ultra-centrifuge with a gradient of sucrose carrying the zones. This seems to me to be a particularly promising development. Similar experiments on cell fragments have recently been described by Holter.[6]

There are other possible methods of separating colloidal substances according to their particle size, even though they may be based upon less fundamental physical properties. This should not be a serious limitation, however, if the separation is more important than the quantitative characterisation of the separated fractions, which after all may be accomplished subsequently by other suitable methods. Thus ultra-filtration is one of the oldest methods of colloid chemistry, and, particularly since through the pioneer work of Elford we learned how to prepare membranes of homogeneous and well-defined particle size, it has proved its usefulness in many applications, particularly in the field of viruses.

A filtration process has of course an " all-or-none " character, that is, a given material will either be held back or pass through. It would appear possible in principle to develop a somewhat

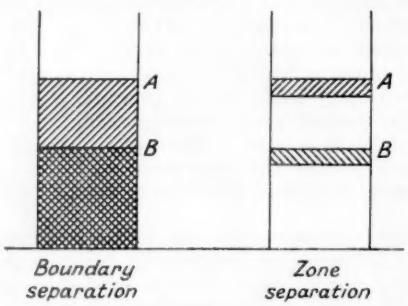


FIG. 1. *The difference between " boundary " and zone separations in electrophoresis, chromatography, sedimentation, and ultra-filtration.*

generalized ultra-filtration procedure in which one would utilize differences in molecular frictional coefficients when a mixture of different substances is forced through a medium offering resistance to their migration. This would, of course, in many cases resemble chromatography, although the retardation of the substances relative to the solvent would depend on friction rather than on adsorption or partition. This possibility was discussed some years ago between Martin, Synge, and myself and Synge and I in 1950 [7] reported some experiments which showed that such effects can be utilized for separation according to molecular size, but it is difficult to obtain pure filtration effects as adsorption also interferes. Another difficulty is to prevent the gel from becoming violently deformed or from collapsing, as rather high pressures have to be used to force the liquid through the thick ultra-filter. It appears that electro-osmotic transport of the medium would be of the best way of avoiding this difficulty, as then the deforming effect of the medium is counterbalanced by the effect of the electric field. As a matter of fact separations which appear to depend in part on filtration have been observed in zone electrophoresis in gels. Mould and Synge [8] have been able to work out a procedure which they call electrokinetic ultra-filtration; this seems however to depend to a considerable extent on adsorption separation according to molecular size. They have applied it with success to the zone separation of polysaccharides related to starch, and of other neutral substances.

I shall turn now to *electrophoretic methods of separation*. which in recent years have had many new applications, particularly in biochemistry. The methods referred to above all depend on particle or molecular *size*, and as electrophoretic migration properties ultimately depend on charge or surface potential it is perhaps not superfluous to point out how necessary

[5] M. G. Brakke, *Arch. Biochem.*, 1953, **45**, 275.
[6] H. Holter, *Experientia*, 1953, **9**, 346, where reference are given to earlier work on sedimentation in gradients.
[7] R. L. M. Synge and A. Tiselius, *Biochem. J.*, 1950, **46**, xli.
[8] D. L. Mould and R. L. M. Synge, unpublished work.

it is in applying separation methods for studying homogeneity to try several different methods in parallel. There are many examples in protein chemistry of substances having almost identical molecular weights but differing widely in electrophoretic properties, and *vice versa*. It is particularly to be remembered that a change in particle size which does not markedly affect the chemical properties has little if any effect on electrophoresis. The most valuable applications of electrophoresis are in biochemistry, particularly among proteins, enzymes, viruses, and similar polar substances of high molecular weight. In recent years, however, the method has found extensive use also for polypeptides, and even simple peptides and amino-acids, and now also for saccharides, and for nucleotides and their constituents. Thus, here again we find that methods which were originally developed for application to colloids and large molecules have gradually and by suitable modifications found important use also with substances of intermediate and low molecular weight. I must admit that I have often been surprised at the very pronounced specificity in electrophoretic properties among biocolloids, which sometimes reflect even species or strain differences (for example, with certain viruses), and recent experiences with peptides in my own and other laboratories also indicate a rather striking specificity in this respect. It is also interesting how frequently mixtures which cannot be resolved by other methods lend themselves to electrophoretic separation. This may often be explained by the fact that components with pronounced electrochemical differences tend to be co-precipitated (especially if they are of opposite charge) in many of the usual fractionation methods, whereas in the electrophoretic separation they remain in solution and thus are allowed to display their differing individual characters.

In the ordinary free " boundary " electrophoresis, taking place in a U-tube with optical observation of the movement of the boundaries, little new in principle has been added to the type of apparatus now in common use in biochemical laboratories. The introduction of interference methods, instead of observation by the curvature of light passing the refractive-index gradients at the boundaries, is of considerable interest and will probably allow investigation of more dilute solutions. Svensson [9] has worked out an arrangement by which a record is obtained of the concentration (interferometry) and the gradient (refraction) on the same plate. As many disturbing factors influence electrophoretic separations at high concentration, it is essential to work at the lowest possible concentrations if clear-cut results are to be obtained.

Perhaps the most important new development in electrophoresis during the last few years is the introduction of zone methods, especially from the point of view of separation. I have already referred to some obvious advantages of zone methods over boundary methods when discussing ultra-centrifugation, and in the case of electrophoresis some further arguments in favour of zone methods may be added. Low concentrations are necessary to eliminate some of the " boundary anomalies " which often interfere seriously in boundary electrophoresis separations. This appears to be achieved more easily in zone electrophoresis, probably because the front and the rear of a zone can be brought much closer together in zone experiments than in the usual U-tube apparatus for boundary electrophoresis. Thus the changes in ionic composition at the boundaries (which always have opposite signs at the front and at the rear) have a chance to neutralize each other by diffusion. This is probably the main reason why in zone electrophoresis one has been able to study a number of substances of low molecular weight (*e.g.*, amino-acids and peptides) which owing to the boundary anomalies it has been difficult or impossible to study by the usual forms of boundary methods.[10]

The fundamental problem in zone electrophoresis—which otherwise requires only a very simple apparatus as no optical observation needs to be made—is to find a suitable supporting medium, without which the zones would be upset by gravitational convections. The most popular medium has been filter paper, no doubt under the stimulating influence of filter-paper chromatography. Paper offers the advantage of easy localization of zones by suitable staining. It is also quite striking how much one can achieve with very simple equipment by zone electrophoresis in filter paper. It has found extensive use in the study of serum and plasma for clinical purposes, and also as a valuable supplement to chromatography in the separation of amino-acids and peptides and for the separation of many other important substances of interest to the biochemist, for example, proteins, enzymes, nucleotides, and other fission products of nucleic acids. Filter paper, however, was not originally made for filter-paper chromatography or electrophoresis and it has some disadvantages which are more evident with proteins than with, for example, peptides and depend on its marked adsorption of many substances, particularly

[9] H. Svensson, *Acta Chem. Scand.*, 1949, **3**, 1170; 1951, **5**, 1301.

[10] For a review of zone electrophoresis, see, *e.g.*, P. Flodin and A. Tiselius, *Adv. Protein Chem.*, 1953, **8**, 1.

those of basic character. Attempts are now being made in the author's laboratory, and elsewhere I believe, to modify chemically the surface properties of the cellulose in the paper to diminish its adsorption, *e.g.*, by esterification or other suitable pre-treatment. I shall not go into detail about the various forms of zone-electrophoresis apparatus but will refer only to an arrangement which has been worked out in Uppsala by Haglund and myself [11] and considerably improved by Flodin and Porath.[12] The electrophoretic separation takes place in a column packed with a suitable filling medium (we use starch or cellulose powder) which forms one limb of a U-tube in an electrophoresis apparatus similar to the common type. After the zones have been electrophoretically separated on the column, this is removed and placed in a fraction collector of the type commonly used in chromatography, so that the zones can be washed out one after the other. The same column can thus be used repeatedly. The apparatus has considerable capacity and has found extensive use in my laboratory also for preparative separation of proteins and other substances.

The methods I have discussed so far have originally been developed for colloidal substances but their use has been, or is being, extended to substances of lower molecular weight. I shall now also mention chromatography where the development has been rather the opposite—from small to larger molecules. It would lead me altogether too far to try to discuss this method here; it must suffice to emphasize how much of the recent development in this field we owe to British scientists. Also I would like to stress that, even though chromatography has its most successful applications to small or medium-sized molecules, it is of the utmost importance in the study of large complicated molecules because of the scope afforded for analysis of complicated mixtures of breakdown products. The separation of colloidal substances by chromatography is a very intriguing problem which so far has met with only partial success. Adsorption chromatography must be based upon an easily reversible adsorption–desorption equilibrium—if not, the process is impracticably slow. Here most proteins fail and in many cases they even become denatured on the surface. With some particularly stable proteins of rather low molecular weight (cytochrome, lysozyme, ribonuclease) ionic-exchange columns have been used successfully by Paleus and Neilands,[13] Hirs, Moore, and Stein,[14] and Tallan and Stein; [15] also hæmoglobin has been chromatographed on such columns.[16] Partition chromatography of proteins has been performed by Herbert and Pinsent,[17] by Martin and Porter,[18] and by Porter.[19] Porter *et al.* have studied extensively the physicochemical background of such separations. The difficulty here is, of course, to find a suitable solvent pair, and we know since the work of Brönsted that it is characteristic of colloids and substances of large molecular weight to collect almost completely in one of the two phases. Brönsted studied the distribution of colloids between two phases a few degrees below their critical point of mixing, where even in such cases the phases are sufficiently similar to give a clear partition. In the author's laboratory it has been found that some proteins lend themselves to chromatography by adsorption promoted by salts added in high concentrations to the solution—this "salting out" adsorption is, however, often not quite reversible. With amino-acids, many peptides, and dyes, salting-out chromatography often works quite nicely. It has also yielded interesting results with very large particles (*e.g.*, Rous sarcoma virus; see Riley [20]). This can perhaps be explained by the greater stability towards denaturation which often characterizes such material, compared with normal proteins.

Adsorbents such as aluminium hydroxide gel, calcium phosphate, and talcum, are often used in preparation of enzymes and other proteins in "batch" operations. They can also be packed into columns when mixed with a suitable filter aid (*e.g.*, Celite). It appears difficult, however, to elute proteins from such columns with sufficient differentiation, and separations are possible only with substances which differ greatly in adsorption affinity. In order to elute a protein zone from such adsorbents it appears necessary to apply an excessively strong eluting agent, *e.g.*, a higher pH or phosphate concentration than would correspond to equilibrium. This is to be expected if the establishment of equilibrium is too slow. The excessive elution

[11] H. Haglund and A. Tiselius, *Acta Chem. Scand.*, 1950, **4**, 957.
[12] P. Flodin and J. Porath, *Biochim. Biophys. Acta*, 1954, **13**, 175.
[13] S. Paleus and J. B. Neilands, *Acta Chem. Scand.*, 1950, **4**, 1204.
[14] C. H. W. Hirs, S. Moore, and W. H. Stein, *J. Biol. Chem.*, 1953, **200**, 493.
[15] H. H. Tallan and W. H. Stein, *ibid.*, 1953, **200**, 507.
[16] N. K. Boardman and S. M. Partridge, *Nature*, 1953, **171**, 208.
[17] D. Herbert and J. Pinsent, *Biochem. J.*, 1948, **43**, 193.
[18] A. J. P. Martin and R. Porter, *ibid.*, 1951, **49**, 215.
[19] R. Porter, *ibid.*, 1953, **53**, 320.
[20] V. T. Riley, *Science*, 1948, **107**, 573; 1949, **109**, 361; *Proc. Soc. Exp. Biol. Med.*, 1950, **73**, 92; *J. Nat. Cancer Inst.*, 1950, **11**, 199, 215.

tends to wipe out the differences in rates of migration of the zones on the column and usually results in bad separations.

In some recent experiments on protein chromatography on calcium phosphate–Celite columns (not yet published) the author has found that strongly adsorbed proteins show a pronounced mutual displacement which gives fairly good separation even at the top of the column, before development has been attempted. Each zone will tail off somewhat into the zone on top of it, but if only a small volume of the solvent is added a typical displacement " procession " of pure zones will result. This is due to the fact that the tailing material in each case is surrounded by material which on account of its higher adsorption affinity acts as a displacer and therefore gives a much higher R_F to the tailing portion than the R_F characteristic of the main zone itself. The tailing material will therefore easily catch up with the zone to which it belongs. Development should not be carried beyond this point, but the column is then cut into segments corresponding to the zones and each segment is eluted with a strong eluting agent. The process can easily be demonstrated with coloured proteins, *e.g.*, with a mixture of serum albumin and carbon monoxide hæmoglobin.

So far, no general method of protein chromatography has been worked out which in any way compares in usefulness with the manifold applications of this highly specific method to substances of lower molecular weight. There is no doubt, however, that the importance of the problem will stimulate many more attempts in this direction. The specificity of adsorption may nevertheless be utilized in other ways for separation purposes, and the use of adsorbents in preparative work, particularly in biochemistry, offers many examples but is of course largely based on empirical principles. Foam analysis and methods analogous to flotation in the fractionation of ground ores and minerals seem to offer interesting possibilities, but with biocolloids again the risk of surface denaturation is appreciable.

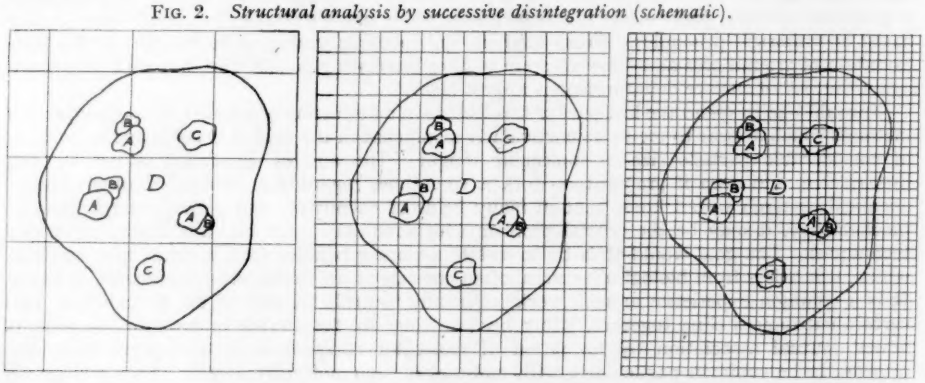
I would like to spend the last part of this lecture in a discussion of some aspects of separation methods which appear to me to be particularly significant in the field of colloids and substances of considerable particle size or molecular weight. The aim of separation is usually first preparative, and even if preparative work is sometimes regarded as inferior to other lines of chemical research we all know that in many fields of chemistry, and perhaps particularly in biochemistry, it may be the crucial problem which requires great skill and highly developed techniques. The goal would thus be to isolate a pure substance from a crude raw material, which, if it arises from biological sources, often consists of an extremely complicated mixture. It is a common experience in such work, especially towards the end of the preparation, that certain substances cling together, either because they are too similar or for other reasons, of which mutual association by formation of molecular compounds or adsorption complexes appears to be common particularly with material of high molecular weight. Such tenaciously held impurities are a great source of annoyance on the road to a pure substance, but one may look at this from a somewhat different point of view.[21] Living matter is highly organized and this organization is a condition for the proper interplay of all those chemical processes which determine life. From a chemical point of view, this organization means that certain substances are localized together, sometimes even linked together, in one way or another in the cell. It is difficult to conceive a mechanism for the most important biochemical reactions in living matter, *e.g.*, the coupling of essential enzymic reactions, without assuming some direct or indirect specific association. Many of the substances which we extract from biological material and which we use, for example, as pharmaceuticals with specific action on the human organism would seem to serve an important function also in the organism from which they are derived, but of this we often know very little. It would be a great help if we knew at least the immediate surrounding of such substances in the living cell. This is, of course, in the first place a problem for the cytochemist and much has been achieved in studies of the distribution of substances in the cell by microscopy, electron-microscopy, and microdissection in combination with ultramicrochemical methods applied to individual cells. However, it is clearly desirable to be able to do such work on a larger scale, obtaining structural information by averaging a large number of identical or nearly identical cells and at the same time isolating the structural fragments in quantities necessary for a detailed study of their chemistry both from a structural and a functional point of view. Naturally such procedures would often have value only as a supplement to the methods based on direct microscopic observation, but to my mind there is no doubt that methods which would allow us to undertake detailed analysis of structural fragments derived from cells or tissue would be of immense importance for the progress of biochemistry. The isolation of particulate elements from cells such as cell nuclei, mitochondria, microsomes,

[21] A. Tiselius, *Chem. Eng. News*, 1949, **27**, 1041.

etc., is of course a step in this direction and has already led to very interesting results. Here we deal with preformed fragments which are comparatively easy to isolate by the methods now at our disposal.

The point I wanted to make here is that the systematic study of particles down to colloidal dimensions, obtained by *successive* disintegration of a large number of cells of other particles, all of a similar structure, is in principle capable of giving us a fairly detailed picture of the original structure at the same time as it involves isolation of sizable quantities of the structural elements in general. To illustrate this I shall give a very simple example, which is entirely schematic. Suppose we have a large number of identical cells consisting of a medium D in which we have form elements of substances A, B, and C, which are different and distinguishable (Fig. 2). Let us suppose that all these cells are disintegrated successively and that the resulting particles can be fractionated into classes each containing particles of approximately equal size by some suitable method. By comparing the three Figures you will see that only with the finest disintegration the majority of the particles will be pure A, B, C, or D, whereas in the first and second case most of the particles will be of mixed composition (in the second case A and B will occur together in many particles but never together with C, whereas in the first case A, B, and C may occur together and, of course, with D). Roughly speaking the particle size, at which two substances segregate, *i.e.*, cease to occur together in the same particle, gives a measure of the distance between these substances in the original structure. If we are able to fractionate

FIG. 2. *Structural analysis by successive disintegration (schematic).*

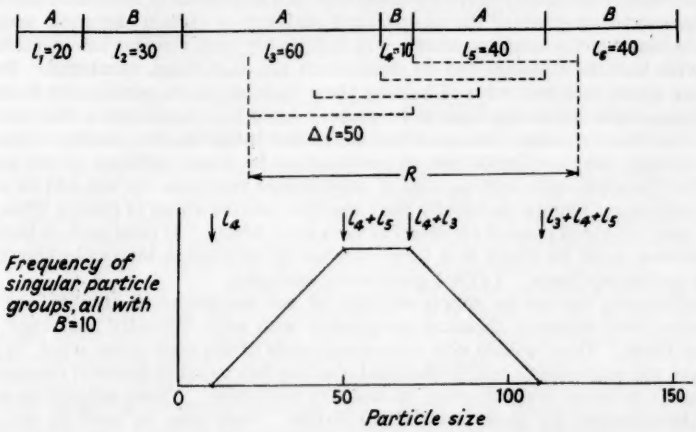


the particles in each size class according to their chemical composition (*e.g.*, by their density) we can deduce not only a rough sketch of the structure derived from the observations just indicated, but, in fact, a complete average picture of the original structure. A simple statistical treatment based upon a knowledge of the frequency distribution of the chemical composition with reference to two substances (say A and B) in each of a number of size classes of successively smaller size would generally be capable of providing us with almost complete information as to how A and B were distributed in the original structure, measured from some easily defined point of origin. It would lead too far to discuss this " puzzle analysis " in detail here. Some simple linear models may serve to illustrate the essential points. A line consisting of segments of substances A, B, C, D, E . . . of different lengths, none of them occurring more than once, is the simplest case. By sufficiently fine grinding we should obtain chiefly homogeneous particles consisting of pure A, B, C, D, E, etc., the relative amounts giving the relative lengths of the segments. Somewhat courser grinding will give us particles containing A and B, B and C, etc., from which the sequence is deduced. A linear model of the type *ABABABABA* requires a more detailed investigation, as shown in the example given in Fig. 3. A random disintegration of such a model does not give a random distribution of particle composition, but also here singular frequencies of constant composition occur in each particle-size class. Again the smallest particle sizes will contain only A or only B, but also in the larger sizes appreciable quantities of particles have constant composition with respect to A and B. This is seen in Fig. 3 if we let the linear element $\Delta 1$, representing a particle size of 50, move along the model to a number of different positions, as indicated by broken lines. All of these will give the same percentage of A and B in the particle. Any segment B which on each side has A, and any segment A which on each side has B will give rise to such singularities in the frequency

of composition. If we plot all singular frequencies containing $B = 10$ as a function of particle size we obtain the curve shown in the Figure. The position of this curve on the abscissa is entirely determined by the size of the two immediate neighbours of l_4 and thus these can be read from the curve, as indicated. By a similar treatment of the other singular frequencies the entire structure of the original model is derived. Thus if it were possible to fractionate the disintegrated material into particle-size classes covering a suitable range, and to sub-fractionate some of these further, *e.g.*, according to density (if A and B are different in this respect), the singular frequencies should stand out as large groups of particles having the same density. We only need to know the composition of a limited number of such singularities to deduce the whole structure, as each of them will contain one complete segment of either A or B, and parts of the neighbouring segments, which is all we need to complete the puzzle.

The singular frequencies are also highly significant in the analysis of two- or three-dimensional models and seem to offer the simplest approach to a solution of the problem, based upon data

FIG. 3. *Puzzle analysis of a linear model.*



which it may be possible to obtain in actual experiments. I have hesitated somewhat to enter upon such speculations in this lecture as we have far too little experimental evidence as yet to show that such an analysis is practicable. Nevertheless it seems to me extremely interesting that, in principle at least, the systematic fractionation of colloids according to particle size and chemical or physical properties of the material of which the particles consist may form the basis for a detailed knowledge of structures of a type too irregular to lend themselves to analysis by X-rays or similar methods. At the same time the colloid methods can provide us with structural elements in sizable quantities for further study of their chemical properties. To a certain extent such a " puzzle " procedure is analogous to methods used in the elucidation of the structure of proteins, as, for example, when Sanger from an identification of the products of partial hydrolysis was able to deduce the sequence of amino-acids in the polypeptide chains of insulin.

These speculations had their origin in some difficulties in biochemical preparations, of which I shall mention only the purification of protein hormones like ACTH. Here we encounter some of the most difficult separations so far experienced in protein chemistry and it seems that to a certain extent this may be due to formation of complexes by several different hormones with each other. If this occurs also in the original material, it may be of significance from a biochemical and physiological point of view.

I do not know if it is quite polite to the Society to conclude this lecture with a plea for an increased interest among chemists in the *impure* substances, but those of you who agree with my argument will admit, I hope, that many obstacles may be turned to advantage if this is kept in mind in work on the separation of colloids of biological origin.

The Chemistry of Intermolecular Compounds.

TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON THURSDAY, NOVEMBER 20TH, 1952, AND AT THE UNIVERSITY, MANCHESTER, ON TUESDAY, FEBRUARY 3RD, 1953.

By H. M. POWELL.

THE production of new chemical compounds has for some time been guided by the concepts of the chemical elements and of the atom, and by the basic idea that new substances are formed when atoms of the elements unite or rearrange in various ways to give molecules or other aggregates.

Theories of chemical combination concerning the manners in which these changes occur derive some of their usefulness from the limitations that they set to combining power. Thus Dalton's laws, modified and re-interpreted but still not to be lightly disregarded by those who would make new compounds, state restrictions on the combining proportions of the elements. The electronic theory of valency may be summarised in a statement of the restriction that atoms unite only in ways that produce the comparative stability of certain electronic arrangements, notably those found in the inert gas atoms. In this theory each element has its electrons numbered and with that its valencies and its compounds are, in a sense, numbered. But the discovery of new atoms and new ways of holding them together seems continually to increase the number of compounds which have yet to be made. Amid the uncertainties that such developments introduce there remains the conviction that some things do not combine chemically and that, in particular, there are limitations on combination by simple addition of one substance to another. The paraffins, although capable of substitution reactions, do not add to other molecules; the noble gases remain chemically inert and the chlorine atoms of carbon tetrachloride do not donate their unshared pairs of electrons to form more bonds. If rules such as these are to be retained, account must be taken of a large number of crystalline intermolecular compounds which seem to disobey them. Table 1 gives some examples.

These substances, formed by simple addition of one compound to another, are sometimes distinguishable from ordinary chemical compounds with such difficulty that they have been mistaken for them. They include now even compounds of the inert gases argon, krypton, and xenon. They are attributable not to chemical bonding but to other forms of interactions, such as are sufficient to cause crystallisation of ordinary molecules. These substances may be isolated and characterised by their physical properties. They may be used in the traditional chemical processes of preparation, purification, identification, and quantitative analysis, and their chemical properties may differ to some extent from those of their components. Their existence has simplified some otherwise difficult chemical operations and many further applications will develop. Discussion as to whether they should be called compounds is profitless and any doubts are best not answered but evaded by the use of suitable qualifying words. In specimen tubes they look much the same as other crystalline compounds. Understanding of their nature is needed to explain their properties and behaviour and to control their effective use.

There have been descriptions of individual compounds of this kind for over a century but it is now desirable, and in a limited way possible, to supplement empirical knowledge by more general statements concerning what is here called their chemistry and to look for principles corresponding to the rules of interatomic chemistry. Such a system should say which molecules will unite and which will not. It should deal with combining proportions, the properties and conditions of formation of the intermolecular compound, and its stability and energy relationship to the components.

The advantage of a system for determining which pairs of substances will form addition compounds may be seen from consideration of all imaginable combinations. If each of the n possible different chemical molecules could unite with every other in one way only, the number of compounds formed would be approximately $\frac{1}{2}n^2$.

Any two approaching molecules experience attractive forces and in certain conditions very little attraction is necessary for intermolecular compound formation. Accordingly there is the hope or fear that many of the $\frac{1}{2}n^2$ possible compounds may exist. These feelings may be encouraged by the reflection that some of the known combining pairs such as urea and straight-chain paraffins seem, from the ordinary chemical viewpoint, most unlikely partners and may never have been brought together with intent. Further when any given pair of substances has at some time been in contact failure to form a compound may be due to unsuitable conditions. For example, quinol in aqueous solution is oxidised by atmospheric oxygen but a hot ethanolic

TABLE 1.

Molecular compounds, AB

A	B	Composition
Deoxycholic acid [1,2,3]	Fatty acids, *n*-paraffins, and some other substances	A_mB, m = **1**, **3**, **4**, **6**, or **8** increasing as length of fatty acid molecule increases
4 : 4′-Dinitrodiphenyl [4]	4 : 4′-Substituted diphenyls	A_mB, m = **5**, **4**, **3½**, or **3**, being the larger the greater the length of molecule B
Urea [5,6]	*n*-Paraffins	A_mB, $m = 0{\cdot}6848(n - 1) + 2{\cdot}181$ where n is the number of carbon atoms
Thiourea [7]	Some branched paraffins and derivatives of *cyclo*paraffins	A_mB; m in general increases with the molecular length of B, but for some sets of three successive members of homologous series m may remain constant at integral values, *e.g.*, **6** and **9**
Quinol [8]	MeOH, MeCN	A_3B
Quinol [8,9]	H_2S, SO_2, HCl, HBr, HCN, CO_2, C_2H_2, N_2, O_2, A, Kr, Xe	Limiting formula A_3B, but variable composition with less B
$Ni(CN)_2,NH_3$ complex [10]	Benzene, thiophen, and a few similar molecules, but not their homologues	AB
Water [11,12,13]	Gas hydrate-forming molecules, *e.g.*, A, Kr, Xe, CH_4, Cl_2, CH_3Cl, $CHCl_3$	$M,(H_2O)_m$, m = **5**—**8** or **16**—**18**, the larger molecules having the higher hydrating numbers

solution subjected to a pressure of 50 atmospheres of oxygen deposits,[14] on cooling, the clathrate compound $3C_6H_4(OH)_2,O_2$. Similarly urea and paraffins do not unite merely on contact, but will do so in presence of methanol. It is not immediately obvious which molecules will unite in this way, but large numbers of related compounds may arise from the discovery of the manner of formation of one of them. Many such series of compounds remain to be found.

Of outstanding importance is a study of the crystal structures of these molecular compounds which may not exist apart from the crystalline state. It is found by this means that the components of some intermolecular compounds are not joined by chemical bonds of any kind. The distances between adjacent atoms in neighbouring molecules are too great. They correspond to non-bonded distances. Thus in the argon–quinol compound the smallest argon-to-CH distance is 3·8 Å. The energy of formation confirms this. Evans and Richards,[15] from the heats of solution of β-quinol and argon–β-quinol clathrates of various compositions find ΔH = **6** kcal. for the heat of formation from gaseous argon and solid β-quinol. This is perhaps larger than would be expected for van der Waals interaction but is explained by the very large number of contacts made by one argon atom with the surrounding structure.

Thus it is certain that from a mixture of A and B molecules which are incapable of chemical union, in certain cases there will be formed a molecular compound of the two in preference to pure A or B. It is perhaps normally expected to be otherwise. A set of molecules, all capable of mutual attraction which is not markedly directed in space seem likely, in general, to crystallise in a close-packed structure as the most stable form. This is in accordance with experience concerning the structures of pure substances, and it may be thought that good packing is achieved most readily when molecules of only one sort are deposited from a mixture. But in some circumstances crystallisation of the pure components may be expected not to occur. Either A and B are strongly attracted or there may be difficulties of packing. The two effects may operate together.

[1] Rheinbolt, *Annalen*, 1927, **451**, 256.
[2] Go and Kratky, *Z. physikal. Chem.*, 1934, **26**, *B*, 439.
[3] Giacomello, *Atti R. Accad. Lincei*, 1938, **27**, 101; *Gazzetta*, 1939, **69**, 790.
[4] Rapson, Saunder, and Stewart, *J.*, 1946, 1110.
[5] Schlenk, *Annalen*, 1949, **565**, 204.
[6] Smith, *Acta Cryst.*, 1952, **5**, 224.
[7] Schlenk, *Annalen*, 1951, **573**, 142.
[8] Palin and Powell, *J.*, 1948, 815.
[9] Powell, *J.*, 1950, 468.
[10] Rayner and Powell, *J.*, 1952, 319.
[11] von Stackelberg, *Naturwiss.*, 1949, **36**, 327.
[12] Clausen, *J. Chem. Phys.*, 1951, **19**, 259, 662.
[13] Pauling and Marsh, *Proc. Nat. Acad. Sci.*, 1952, **38**, 112.
[14] Evans and Richards, *Nature*, 1952, **170**, 246.
[15] *Idem*, personal communication.

Attraction between particular parts of the two molecules will require their proximity in the crystal structure. Each atom of one molecule will be intricately bound up with its surroundings, and as with some other complex structures, the ratio of A to B molecules will be simple. Whatever the nature of the intermolecular attraction, this may require a simple molecular ratio which in itself is not evidence for the integral combining power associated with chemical-bond formation. Among the molecular compounds in which special attractions between the component molecules are operative may be numbered some, though not necessarily all, of those formed between aromatic polynitro-compounds and other aromatic molecules. Various categories of interacting pairs have been considered recently by Mulliken.[16] The intermolecular compounds considered in this Lecture are those in which special interactions are not of such importance. Their crystal structures are of a different kind; frequently one component forms a framework of some sort which encloses spaces, either open or closed in which the second component is held. The first component forms an open structure, but the two together are more closely packed.

Spaces of this kind may arise in several ways. Intermolecular spaces are left when globular molecules are in closest packed array. The dimensions of the holes are proportional to those of the molecules, and for large molecules would be of a size capable of containing smaller molecules of a second component.

The molecule itself may have a cavity. This is the case in the large ring systems of α-, β-, and γ-dextrin.[17]

Molecules of one component may be subject to strong mutual attractions and these may be directed in space in such a way as to produce an open structure, just as hydrogen bonding causes the open crystalline structures of resorcinol or ice. An open structure, formed by such a substance may have vacant spaces large enough to contain molecules of a second component if these are available. β-Quinol which may be obtained in suitable conditions may be so regarded although the normal form, α-quinol, has a different crystal structure. In other cases the framework structure has no separate existence, but is formed only in the presence of the second component. For example, urea under the influence of strong attractions between NH_2 groups and the oxygen atoms of neighbouring molecules normally forms a structure which is not closely packed. In presence of straight-chain hydrocarbons, and a little methanol as solvent, it forms a much more open structure which clearly could not exist on its own. The urea molecules are tightly bound to each other—perhaps more so than in urea itself—and stability arises from the enclosure of the long paraffin in the channels. Similarly in gas hydrates, water molecules are linked to form cages not found in ordinary ice.

In the examples mentioned there is a type of linkage between molecules of the one component, *viz.*, hydrogen bonding which may be reckoned as a chemical interaction. But any type of intermolecular attraction, if it is strong enough, may have a similar effect. Van der Waals forces may be sufficient.

The open structure thus formed is often common to a series of compounds. The second component may be varied in character much more than the first, provided it meets the structural requirements imposed by the almost constant pattern of its partner.

Examples include those in which molecules of one component are located in channels or closed cavities in the structures formed by the other component. These are convenient categories but there is no precise dividing line; a set of adjoining cavities differs only in degree from a channel. Further, whether a space is to be considered as closed depends on what is being enclosed.

Part of the question concerning which pairs of molecules will form intermolecular compounds of this kind is answerable. Which molecules will form enclosing structures is not obvious, but, when such a structure is known, the nature and number of enclosable molecules can be understood and in part predicted. In all cases the enclosed molecule must not be too large for the available space. Some possibilities will now be considered.

A Three-dimensional Framework encloses Cavities of Limited Size.—There are strict limitations on the shape and size of the enclosed molecule. Of two chemically related molecules, *e.g.*, two members of a homologous series, one may be enclosed but the other excluded by its great dimensions. Too small a dimension may also result in no compound. Examples are provided by the clathrate compounds of quinol which have cavities capable of containing molecules chemically as diverse as sulphur dioxide, formic acid, methanol, hydrogen chloride, nitrogen, cyanogen chloride, and xenon. Homologues such as ethanol and other large molecules do not form similar compounds. The helium atom is too small to do so. In this case there is a definite numerical ratio of cavities to molecules of the enclosing structure. Since each cavity can hold no more than one

[16] Mulliken, *J. Phys. Chem.*, 1952, **56**, 801.
[17] Freudenberg and Cramer, *Chem. Ber.*, 1950, **83**, 296.

molecule there is a limiting composition with a maximum ratio of enclosed to enclosing molecules. Although this cannot be exceeded there may be lower values when some of the cavities are unoccupied. Molecular compounds of this kind may therefore obey a law of definite proportions or they may not. For the quinol clathrates all the spaces are filled when the substance to be included, *e.g.*, methanol or methyl cyanide, is used as the solvent for crystallisation, and a ratio such as 3Quinol : MeOH results. When, as in the case of argon and other substances, an indifferent solvent for quinol and the enclosed substance has to be used, and a sufficient concentration of gas perhaps achieved only by raising the pressure, a number of holes may be left vacant. The number of vacant spaces is variable and depends on the molecules available for enclosure when the cage is formed. The ratio of the two components in this case is not simple.

A similar maximum ratio of enclosed to enclosing molecule and a size limitation for the enclosed component are found in the gas hydrates. There have been modifications of detail in the structural interpretation but as a general concept it is agreed that the hydrating molecules are packed into spaces in ice-like lattices. The " ice " forms, unlike ordinary ice, are cubic, and whole groups of hydrates have a common type and size of unit cell. The voids are of various sizes and co-ordination numbers. A cubic cell of side $a = 12$ Å and hydrating numbers about 5—8, are found for a group of small-molecule hydrates, and another group of larger molecules has hydrating numbers 16—18 and a unit cell of 17 Å. For the 12-Å type Clausen [12] makes the basic void an undeformed pentagonal dodecahedron of water molecules, co-ordination number 20 (for small molecules); and a medium void for somewhat larger molecules has 12 pentagonal and 2 hexagonal faces, co-ordination number 24. A unit cell has 46 water molecules. There are 6 small voids and 2 medium voids. Hence the ratios of molecules may be $46 : 6 = 7\frac{2}{3} : 1$ (medium) or $46 : 8 = 5\frac{3}{4} : 1$ (small). The size of the hydrating molecule determines which voids are filled. Table 2 gives hydrating numbers for two groups of molecules.

TABLE 2. *Ratios for gas hydrates.*

Small molecules		Medium molecules (some smaller voids not filled)	
Gas	H_2O	Gas	H_2O
A	4·5	C_2H_6	7
CH_4	6·3	C_2H_4	7·4
C_2H_2	5·7	C_2H_5F	8·27
PH_3	5·9	SO_2	8
H_2S	5·7	CH_3Cl	7·2
CO_2	6	Cl_2	6·91
N_2O	6	Br_2	10
H_2Se	5·87		

Some points in the chemistry of intermolecular compounds are illustrated by the clathrates and the gas hydrates. Thus no great attraction exists between the molecules of the two components. Indeed, for the formation of this kind of compound, not only is small intermolecular action possible but it seems to be essential. Those molecules which form gas hydrates are as a rule hydrophobic. A hydrophilic molecule, *e.g.*, HCl, will combine with water to make a hydrate of a different sort. Aldehydes, alcohols, acids, amines, amides, and various other molecules which are capable of hydrogen-bond formation do not form gas hydrates and, in general, substances easily soluble in water do not form them even if their molecular size is favourable.

Since the form of attraction between the components is thus mainly of the general van der Waals type, it acts in a very indiscriminate way and mixed compounds may be formed, some cavities containing one enclosed molecule, some another.

The comparatively slight attraction between cage and occupant is manifest in another way. The enclosed molecule may be capable of rotation or other movement in its cavity or may occupy statistically different fixed positions in its cavity. This has been found directly by Fourier analysis, which shows sulphur dioxide to be in rotation about one axis in its quinol cage. The dielectric properties of some other clathrates lead to similar conclusions concerning the motion of imprisoned molecules.[18] The poor *X*-ray scattering by the gas hydrates indicates similar freedom of motion for them in their " ice " cavities.

Channels in a Three-dimensional Structure.—If the channels can be regarded as cylinders or other spaces which are uniform along their lengths the enclosable molecules must be of suitable, restricted cross section but their length is not limited. Thus members of homologous series may behave similarly. Examples are found in the urea–*n*-hydrocarbon adducts and related compounds.

[18] Dryden and Meakins, *Nature*, 1952, **169**, 324.

In this case the composition may be definite although the molecular ratio is not simple. The number of enclosing molecules necessary to surround a given molecule of *n*-paraffin can be calculated from the known dimensions of the cell, the number of urea molecules it contains, and the dimensions of a paraffin together with the intermolecular spacing between two paraffin ends. Thus Smith [6] gives the length of hydrocarbon chains as $[1{\cdot}256(n - 1) + 4]$ Å (for n odd and nearly so for n even). Since $c = 11{\cdot}01$ Å and corresponds to 12 ureas and 2 channels, U/H, the molecular ratio urea : hydrocarbon, is given by

$$\frac{U}{H} = \frac{12[1{\cdot}256(n - 1) + 4]}{2 \times 11{\cdot}01} = 0{\cdot}6848(n - 1) + 2{\cdot}181$$

If the channels are not uniform we may expect departures from this type of equation. This is the case for the thiourea adducts [7] with ωω′-di*cyclo*hexylalkanes. Thiourea adducts differ structurally from those of urea but there is a general resemblance between the two series. The channels are, as might be expected, larger. To fill them it is necessary to have molecules thicker than the normal paraffins. That the principle of good space filling, under the influence of van der Waals attraction, is of basic importance in these compounds is made clear by the non-existence of *n*-paraffin–thiourea compounds. Branched paraffins form adducts, and a similar rule for composition in relation to molecular length applies. But the thiourea channels are less uniform in character than those in urea and there are marked periodic variations in attractive forces. Accordingly the adducts with ωω′-di*cyclo*hexylalkanes do not show a continuous variation of molecular ratio with increase in length of the paraffin chain.

Chemical Purification by Means of Inclusion Compounds.—The dimensional limitations of the spaces in inclusion compounds suggest chemical uses in separation and purification processes. The principles are simple. The space of fixed shape and size will contain only certain molecules. From mixtures, therefore, one molecule may be taken in and another not. In clathrates there are severe limitations, and homologues are separable. In channel structures homologues are not separable, but branched and straight forms may be separated. *cis*- and *trans*-Isomers may be separated. The possible variations are endless but need individual study.

In practice the matter may not be quite so simple. A molecule which does not normally enter the urea or thiourea channels may do so when accompanied by another substance which normally goes in. Conversely a compound that normally forms a complex may be prevented from doing so by the presence of one that does not.[19]

The complex $Ni(CN)_2NH_3,C_6H_6$ has been used to obtain benzene of 99·992% purity in large yield.[20]

Tri-o-thymotide.—The substance tri-*o*-thymotide recently discovered by Wilson Baker, Gilbert, and Ollis,[21] illustrates many of the points which have been mentioned. Tri-*o*-thymotide crystallises with one-half of a molecule of *n*-hexane, chloroform, or several other substances. An *X*-ray investigation [22] showed that tri-*o*-thymotide, which has a molecule of rather awkward shape, will crystallise by itself from some solvents, but that from many others it crystallises in a solvated form. For some of these compounds the solvent, which may ordinarily be very volatile, is removed only on heating at 180° in a good vacuum. Examples are the compounds with benzene, chloroform, and *n*-hexane.

The crystal structures of these compounds are not all the same but they fit into several groups. A large number of small molecules give trigonal crystals with an almost constant form of unit cell. Molecules in this class are *n*-alcohols up to pentanol, and a number of other short molecules such as *n*-propyl iodide, acetone, *sec.*-butyl bromide and iodide, active amyl alcohol, carbon disulphide, chloroform, ethylene dibromide, and benzene. There is little doubt that hundreds of other substances of suitable molecular dimensions could be similarly included. The detailed crystal structure is not known but certain inferences can be drawn. The general behaviour is similar to that of clathrates or urea adducts. The chemical nature of the included molecule seems of little importance. Its size is. The spaces in which the included component lies seem to be of limited length. Thus *n*-hexane, *n*-hexanol, *n*-heptanol, *sec.*-octyl and cetyl bromide, all of which have longer molecules than those previously mentioned, give molecular addition compounds, but these have a different symmetry. They are, however, rather similar in unit-cell dimensions and, like the trigonal compounds, contain six molecules of the main tri-*o*-thymotide component, related to each other by three-fold screw-axes of symmetry. Thus it

[19] Linstead and Whalley, *J.*, 1950, 2987.
[20] Evans, Ormrod, Goalby, and Staveley, *J.*, 1950, 3346.
[21] Baker, Gilbert, and Ollis, *J.*, 1952, 1443.
[22] Newman and Powell, *J.*, 1952, 3747.

appears that tri-*o*-thymotide molecules adjust themselves to the longer partners by forming an alternative, though related, structure. Perhaps the cavities give place to channels, or one type of channel to another. Similarly the cavities of the trigonal variety which contain the smaller molecules must be limited in breadth. Bromoform, clearly not too long a molecule, does not form the trigonal structure. Its greater width, compared with that of chloroform, must be the determining factor. This is confirmed by experiments with other selected molecules. A single side-chain substituent such as the bromine atom of *sec.*-butyl bromide, does not broaden the molecule too much for its inclusion. However, *iso*butene dibromide and acetylene tetrabromide were found, as expected, not to enter the trigonal structure. Nor do these broad, but on the whole, short molecules enter the cavities of the hexagonal form which will accommodate molecules as long as cetyl bromide and as broad at least as *sec.*-octyl bromide. Instead, they form molecular compounds with tri-*o*-thymotide which have special structures of their own. The composition is in each case one tri-*o*-thymotide to one other component molecule, and so far each of them is the only member of its structure type. It may be expected that other substances of molecular shapes which it is possible to some extent to select and predict will form related structures.

Structures with Dissymmetric Cages or Channels.—The tri-*o*-thymotide molecule is not identical with its mirror image but may have a form resembling a three-bladed propeller. It can be converted into its mirror image by rotations about the single bonds of the central ring system. The interconversion is sterically hindered. It has been shown from *X*-ray examination and symmetry considerations that pure orthorhombic tri-*o*-thymotide contains equal numbers of *dextro-* and *lævo*-molecules, but molecular compounds of tri-*o*-thymotide with benzene or with *n*-hexane contain molecules of one hand only. The crystals themselves do not reveal this by means of enantiomorphous faces, but the *X*-ray diffraction pattern proves that the space-group is enantiomorphous. These findings have been exploited in chemical operations which lead to separations of *dextro-* and *lævo*-molecules.[23] The tri-*o*-thymotide–benzene adduct has been grown in large crystals. When a single crystal is dissolved in chloroform the solution rotates the plane of polarisation of light. Thus the normally racemic tri-*o*-thymotide has been induced to resolve spontaneously. In solution the rotation disappears rapidly through racemisation of the tri-*o*-thymotide according to a first-order reaction which has a half-life period of about 3½ minutes at 20°. As a result of this rapid racemisation the whole of the tri-*o*-thymotide may be obtained in the *dextro*-form. A single crystal may be grown in a time long compared to the half-life, so that equilibrium of *dextro-* and *lævo*-forms is maintained in solution while the *dextro*-form alone is removed from it. If a nucleus of the opposite hand is used all the tri-*o*-thymotide may be removed in the *lævo*-form. By suitably seeding a cooling solution the whole of the crystalline adduct may be obtained in either the *lævo-* or the *dextro*-form without growing large crystals.

Since the tri-*o*-thymotide framework in the crystal is enantiomorphous the spaces that it encloses in the two kinds of crystals must also be mirror images of each other. When, therefore, an adduct is formed by crystals of the substance from a solvent which is itself a racemic mixture, it would be expected that any one crystal will take in preferentially the *dextro-* or the *lævo*-form of a solvent molecule according to the shape of its cavities. The volume available for the excluded molecule is sufficient but its configuration is wrong. When the experiment is carried out with *sec.*-butyl bromide it is found that crystals of a homogeneous crop, prepared by growth from a single nucleus, will rotate the plane of polarisation of light when dissolved in chloroform. The large rotation due mainly to the tri-*o*-thymotide decays rapidly throughout racemisation and leaves a much smaller permanent rotation due to the *sec.*-butyl bromide. The rotation of the resolved butyl bromide is found to be of the same sense as that of the tri-*o*-thymotide which it accompanies.

By these methods substances have been obtained in optically active form without the use of any optically active starting material in its resolved form. Schlenk [24] has reported similar resolutions by means of urea adducts. They belong to an enantiomorphous space-group but in this case the molecules which form the framework are not dissymmetric. Cramer [25] finds partial optical resolutions in the dextrin adducts. Here the dextrin molecules themselves already exist in optically active form.

[23] Powell, *Nature*, 1952, **170**, 155.
[24] Schlenk, *Experientia*, 1952, **8**, 337.
[25] Cramer, *Angew. Chem.*, 1952, 136.

OBITUARY NOTICES.

JOHN SAMUEL STAFFORD BRAME.

1871—1953.

With the passing of John Samuel Stafford Brame, Petroleum Technology and Chemistry lose a distinguished member of that rapidly diminishing band of pioneers who laid so well and truly the foundations of the first Society concerned with the science and application of mineral oil.

His was the generation of Boverton Redwood, Vivian Lewes, Thomas Holland, Charles Greenway, and John Cadman, all of whom rose to eminence in the service of petroleum science and in the industry. He was president of the Institute of Petroleum in 1921—23. Perhaps his greatest work lay in the direction of standardization. He presided over the meetings of the Standardization Committee of the Institute from 1929 to 1938 and saw it grow in importance year by year, culminating in the friendly co-operation with the American Society for Testing Materials. He contributed many articles to the technical press and wrote a well-known and admirable text-book on Fuel.

He was connected with the Royal Naval College so far back as 1897, when he joined the staff, being promoted to the Chair of Chemistry in 1914—from which he resigned in 1932. In the New Years Honours List in 1930, he was awarded the C.B.E.

He presided with Major Crozier at a Ministry of Transport enquiry into proposals to allow tankers containing motor spirit to pass higher up the river Thames than had hitherto been permitted. In his later years he was on the Board of Alexander Duckham & Co. Ltd. and for many years he conducted evening classes in Petroleum Technology at the Cass Institute.

In all he had an active and vigorous outlook on life. He was invariably cheery and optimistic, a delightful companion and the best of friends.

He was survived by Mrs. Brame for only two days. They were buried together.

A. E. Dunstan.

COLIN CAMPBELL.

1888—1953.

Colin Campbell was born in Manchester on June 26th, 1888, and died at his home there on August 23rd, 1953. At the time of his death he was Dean of the Faculty of Science in the University of Manchester and Assistant Director of the Chemical Laboratories.

Campbell entered the University, where he was to spend his whole career, from William Hulme's Grammar School with a Francis Cartwright scholarship. After graduating with first-class honours in chemistry in 1909, he at once became Schunck research assistant to Professor H. B. Dixon in the field of explosions in gases. His work gained him in 1921 the degree of D.Sc. and he eventually established an international reputation in that field. Some 17 papers, the majority of them published in this *Journal*, describe the results of work over a period of 20 years, at first with Dixon and later with his own post-graduate assistants.

Much of Campbell's research had a distinction that merits a description of it in some detail. In the early period, which covered the First World War when he was a member of Dixon's team of inspectors of explosives under the Ministry of Munitions, his work was related to Dixon's interests as a member of the Home Office Committee on Explosions in Mines. Incombustible dusts were being shown to exert a suppressing action on flames, contradicting the results of Abel 30 years earlier which had seriously delayed the introduction of stone dusting in coal mines; some of Dixon's new experiments were described in Campbell's first paper (*J. Soc. Chem. Ind.*, 1913, **32**, 684). Then followed measurements of the speed of flame in mixtures of coal gas and air ignited by spark in long tubes (with E. L. Sellars, *ibid.*, p. 730), and an account of refinements in the laboratory preparation and analysis of methane (with A. Parker, *J.*, 1913, **103**, 1292). Also in Dixon's laboratory he examined, with negative results, the effect of an intense magnetic field on the progress of the detonation wave in mixtures of various gases with oxygen (with W. E. Slater, *Proc. Roy. Soc.*, 1914, *A*, **90**, 506); he took part in a photographic analysis of the growth of the flame in gases ignited in a tube by adiabatic compression (with L. Bradshaw, *J.*, 1914, **105**, 2027), and in some elaborate direct measurements of the velocity of sound, and hence of the ratio of the specific heats, in various permanent gases (including nitrogen) up to 600° and

in some instances up to 1000° (again with A. Parker, *Proc. Roy. Soc.*, 1922, *A*, **100**, 1). Also with Dixon (*Trans. Faraday Soc.*, 1926, **22**, 307) calculations, according to Jouguet's equations, were reported of the specific heats of nitrogen in the range 4650—5900° based on the velocity of the detonation wave in $C_2N_2 + O_2$ diluted with $\frac{1}{2}N_2$, N_2, and $1\frac{1}{2}N_2$. The effect of nitrogen on the rate of the initial spread of flame in mixtures in which the fuel : oxygen ratio was kept constant was to give a speed directly proportional to the calorific value of the total mixture (with O. C. de C. Ellis, *J.*, 1924, **125**, 1957).

In the subsequent period, when his work was independent of Dixon, Campbell's interest was concentrated on the study of the detonation of gaseous mixtures in glass tubes, mainly by the photographic technique of Mallard and Le Chatelier in use at Manchester since about 1895. For this work, quickly to become widely known, the film camera was a simple drum of cast aluminium revolving on pivot bearings and, although capable with safety of a peripheral speed of no more than 40 m./sec. (to be doubled later), Campbell improved its resolution by increasing the slope of the trace through a corresponding sacrifice of magnification. With this intrument, crude and slow by the present standards set by modern fast film in cameras employing a rotating mirror, he at once obtained results of importance to a better understanding of the structure of the detonation wave. By direct photography only (Schlieren photography had not yet come into routine use) Campbell demonstrated the duplex nature of the wave by separating its elements of concussion and combustion at a point where his explosion tube was abruptly enlarged (*J.*, 1922, **121**, 2483); the records yielded values of the velocities of the shock wave (slow in relation to that of the parent detonation wave) and of the slower-moving flame. Similarly, with a flame accelerating in a cylindrical tube during the period immediately preceding detonation, one or more separate points of spreading inflammation appeared in the unburnt gas, presumably as a result of adiabatic heating in shock waves just ahead; it was to be shown later (with C. Whitworth and A. King, *Mem. Manch. Lit. Phil. Soc.*, 1931—32, **76**, 45) that increased pressure existed in that region. Detonation may arise from one or other of the auto-ignitions ahead at a speed temporarily greater than that characteristic of the gas mixture in use (with D. W. Woodhead, *J.*, 1926, 3010).

It was in the last paper that attention was first directed to a striking and regular banded appearance of a photograph of the detonation of moist $2CO + O_2$, a phenomenon in detonation eventually to become well known as "spin." The bands were bright and remarkably regular, and each was associated with an undulation in the wave-front. The general appearance was very different from the uniform illumination of the smoothly progressing flame-front shown in previously published photographs, and hitherto believed to be characteristic of the detonation wave. However, indicative of a uniform mean speed, a straight edge could be placed against the undulations in the front of a wave of the new type. Dixon himself, then Emeritus Professor, visiting Campbell's room to inspect the new records, made the ingenious suggestion that the negatives had been dried whilst in contact with sheets of the departmental notepaper. The notepaper in use at that time bore a barred watermark that fitted exactly the bands on the negatives! They had however been dried innocent of any such or other contacts, and a scrutiny of Dixon's own negatives of more than 20 years earlier (now almost unmanageably curling) disclosed a number of similar examples, but all of them ill-defined and undetected owing to insufficient photographic resolution (for example, *Phil. Trans.*, 1903, **200**, *A*, 315).

Other experiments were soon described (also with D. W. Woodhead, *J.*, 1927, 1572) showing that the bands were characteristic of the detonation wave in only certain mixtures (sometimes the more dilute ones) of oxygen with CH_4, C_2H_6, C_2H_4, CS_2, and C_2N_2 as well as of all mixtures with CO, although they did not appear in $CO–O_2–H_2$ mixtures that contained more than about 6% of hydrogen. The pitch of the undulations causing the bands was the same in moist $2CO + O_2$ at initial pressures up to 3 atm.; it was however proportional to the diameter of the tube, whilst independent of its length, and an interpretation based on a helical motion of the detonation wave was therefore suggested (at the instance of E. F. Greig). After satisfying himself and many sceptics that the phenomenon was not caused by vibrations of his apparatus Campbell in a third paper of the series (with A. C. Finch. *J.*, 1928, 2094) produced abundant confirmation of a helical motion, either clockwise or anti-clockwise, which applied not only to a luminous head of detonation but also to a long luminous tail lying close to the wall of the tube. Novel techniques were employed in these last experiments, comprising fixed plane mirrors (for rotational phase discrimination) and the directing of the open-ended explosion tube towards the camera, an arrangement which yielded cycloidal traces. A physical demonstration of the helical motion was provided by lightly dusting the interior of the tube with French chalk before firing; a well-defined dark helical track was left in the dust. This last result was promptly repeated, as

was the production of banded records, by W. A. Bone and R. P. Fraser (*Phil. Trans.*, 1929, **228**, *A*, 197; 1931, **230**, *A*, 363); these workers concluded by experiment, and by deduction from fluid mechanics, that the spin does not involve rotation of the gas mass as a whole but only of the luminosity of the head and the tail. Confirmation of Campbell's observations came also from P. Laffitte in Paris who affirmed that spin is characteristic of all mixtures near the limits of detonability.

In only two of Campbell's remaining five papers (in all of which C. Whitworth participated) was he concerned directly with spinning waves. He found them to be more prone than non-spinning waves to damping down either at an enlargement in the containing tube (with A. King, *loc. cit.*, and *Trans. Faraday Soc.*, 1932, **28**, 681), or in a non-rigid section of it. Non-spinning waves could pass through considerable lengths of even thin rubber tubing without appreciable loss of speed. With W. B. Littler, in measurements of pressure in a closed cylinder, Campbell and Whitworth observed that the time to reach maximum pressure appeared to be the same for various mixtures of gases with oxygen at the lower limit of detonability (*J.*, 1932, 339). The same group devised an ingenious method of measuring the pressure in the detonation wave by observing the results (with the drum camera) of interposing copper foils in a range of thicknesses clamped across the explosion tube in the path of the wave (*Proc. Roy. Soc.*, 1932, *A*, **137**, 380); there was reasonably good agreement between the observed and the calculated pressures. A last paper with Whitworth and Woodhead (*J.*, 1933, 59) described a re-determination photographically of the velocity of detonation of the range of CO–O_2 mixtures; the velocity, as with H_2–O_2 mixtures dependent mainly on the density of the mixture and its calorific value, showed a maximum with excess of carbon monoxide (at about the mixture $3CO + O_2$).

The helical interpretation of Campbell's banded type of photograph has not been challenged since the early days after its discovery, when his stone-floored dark room on the basement corridor of the chemistry block in Burlington Street was frequented by the incredulous, staff and students alike. Banded records have been widely obtained and various explanations have been advanced, notably by Bone and Fraser, Becker, Jost, Manson, and Lewis, but no complete theory has even yet been developed. Many questions remain without satisfactory answer: for instance, why do some gas mixtures show bands and others not? More experiments are required on the lines that Campbell himself had begun to work, but with modern high-speed Schlieren and manometric techniques, applying these to the points of incipient and temporary breakdown of a spinning wave, for example, at points of enlargement in the containing tube or of abrupt changes in the composition of the gas mixture (including short lengths of incombustible gas over which Campbell observed that detonation can be transmitted).

It is by "spin" that Campbell's research will be remembered. He will be remembered also for his many high personal qualities, not only by his own few privileged research assistants but also by many generations of students. He had become a member of the staff of the Chemistry Department in 1914 and Senior Lecturer in 1925. He played an important part in the teaching both in the first-year laboratory and in the theatre, where his characteristic lectures were lucid and precise and pointed by frequent experiments. He had the ability to develop a sense of vocation in his students; he never lost a freshness of approach to his day-by-day problems, displaying a friendly serenity in keeping with his love of the high places in Switzerland and the Lake District, where he spent many of his holidays. With his trim figure and brisk walk he was everywhere welcomed; beneath a high forehead his eyes were kindly and wise, and before the warmth of his voice difficulties quickly melted away. It has been said that he was usually the first to learn of a student's personal problems, and those in need were certain to receive sympathy and encouragement to further effort.

Campbell's research work had come to its close in 1935 when he was appointed Assistant Director of the Chemical Laboratories, his activities then covering a much wider field. The guardian of a great departmental tradition, his long influence both in maintaining a unified department through a period of great change, and as a member of the Board of the Faculty of Science, cannot be overestimated. This aspect of his work culminated in his appointment as Dean in 1952.

The religious life of Manchester has been impoverished by Colin Campbell's death. As a Congregationalist he gave a life-long devotion to his own Cavendish Chapel in which he had filled many offices. He had a special interest in the Manchester and Salford Shaftesbury Society. His deep Christianity, prompt friendliness, and a characteristic combination of modesty, patience, and persistence will long be remembered, both in his university and in walks of life outside its walls, by many who are proud to own their debt to him.

D. W. Woodhead.

GERTRUDE MAUD ROBINSON.

1886—1954.

It was with a profound sense of loss that chemists, both in this country and overseas, learnt of the sudden and unexpected death on March 1st of Lady Robinson. Few chemists have been held in greater esteem and affection.

Lady Robinson, *née* Walsh, was born on February 6th, 1886, being the daughter of Thomas Makinson Walsh and Mary Emily Walsh, *née* Crosbie. After attending Verdin Secondary School, Cheshire, she entered Owens College, then a constituent College of the Victoria University of Manchester, in 1904, graduating with the degree of B.Sc. in 1907 and proceeding to M.Sc. in 1908. After graduation she commenced research in organic chemistry with Dr. C. Weizmann, later President of Israel. This was the beginning of a lifelong friendship with Dr. Weizmann and his family. It soon became evident that Miss Walsh, as she then was, had experimental skill of a high order and in collaboration with Dr. Weizmann she published two papers (*J.*, 1910, **97**, 685; 1911, **99**, 448), the former dealing with derivatives of 1 : 4-dichloroanthraquinone and the latter with the preparation and properties of two unsaturated hydrocarbons, 2-methyldodeca-1 : 3-diene and 2-methyldeca-1 : 3-diene. Her work in the Manchester laboratories was however interrupted by her marriage in 1912 to Dr. (now Sir) Robert Robinson, at the time an assistant lecturer and demonstrator in the University, and her departure with him to Australia on his appointment to the Chair of Organic Chemistry in the University of Sydney.

In spite of her numerous preoccupations as a wife and mother, Lady Robinson throughout her life continued to be an indefatigable laboratory worker. She was the author or joint author of some thirty memoirs many of outstanding importance. Thus she suggested (*J.*, 1917, **111**, 109), independently of Angeli, that the aromatic azoxy-compounds had the now accepted asymmetric structure and, in a later paper (*J.*, 1924, **125**, 827) in collaboration with her husband, she provided an interpretation of the mechanism of the Fischer indole synthesis, which followed an earlier paper (*J.*, 1918, **113**, 639) on the synthesis of tetraphenylpyrrole. Subsequently her main interests were largely in the chemistry of the higher fatty acids and the plant pigments. In the former field she was the first to synthesise oleic acid and the 6-oxostearic acid (lactarinic acid), occurring in species of the fungus *Lactarius* (*J.*, 1925, **127**, 175). This important synthesis of oleic acid would appear to have been overlooked in recent reviews. This was followed by the publication (*J.*, 1926, 2204; 1930, 745; 1934, 1543) of an elegant general method for the synthesis of the higher fatty acids, both saturated and unsaturated, culminating in the preparation of tricontanoic acid, $C_{30}H_{60}O_2$, and 13-oxodotetracontanoic acid, $C_{42}H_{82}O_3$, which were at the time probably the fatty acids with the highest molecular weights which had been synthesised. The methods developed by Lady Robinson have been largely used by other investigators.

It is probable, however, that Lady Robinson found her greatest interest in the study of the plant pigments. This was due, not only to the fact that they exercised to the full her great experimental skill, but also because of the pleasure which she found in her garden. Ample evidence of the latter interest was to be seen in her beautiful Oxford garden. The impetus to the study of the plant pigments was doubtless Sir Robert Robinson's syntheses of the anthocyanins. Space will not permit of a detailed account of this work, which appeared in five long memoirs (*Biochem. J.*, 1931, **25**, 1687; 1932, **26**, 1647; 1933, **27**, 206; 1934, **28**, 1714; 1938, **32**, 1667) and reference can only be made to the more salient features; it is however likely to have a marked influence on plant genetics (*J. Genetics*, 1939, **37**, 378). Lady Robinson was the first to observe that the colour of the flowers did *not* indicate the pH of the cell sap. Thus, for example, the sap of the blue cornflower was, contrary to expectation, acid, a very significant observation in a heterogeneous system. She discovered also that the so-called co-pigments, which are tannins and flavonols, exercised a marked influence on the pigments' colours (*J. Amer. Chem. Soc.*, 1939, **61**, 1605, 1606). Perhaps her most important contribution was her proof of the wide distribution of the leucoanthocyanins which she found to be present in the lignins. This is still largely an unexplored field. Sir Robert Robinson has mentioned to me in conversation that Lady Robinson was especially interested in the leucoanthocyanins because it was entirely her personal contribution and she was convinced that they played an important part in vegetable physiology.

During the course of these investigations use was made of partially miscible solvents for the

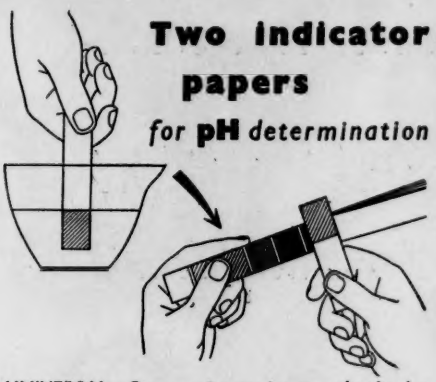
separation of the various plant constituents. This was actually an anticipation of modern partition separation methods.

After the outbreak of war the resources of the Dyson Perrins Laboratory were devoted to a study of the penicillin problem. Lady Robinson was actively associated with this work and I recollect learning during a visit to Oxford that she had prepared for the first time a synthetic material with penicillin-like antibiotic properties. This was a notable contribution. She had been previously investigating a problem of biochemical importance and for the last 10—15 years she was engaged, in association with Dr. T. B. Heaton, in the attempted isolation of a substance having growth-inhibiting properties. Unfortunately this work has not been completed and only very brief accounts have been published (*Nature*, **1943**, **151**, 195; **1948**, **162**, 570).

It might be thought that this intense scientific activity, which has been presented in brief outline, would have fully occupied Lady Robinson's time. This was however far from being the case. She shared to the full her husband's scientific and other interests. She was a skilled climber and travelled widely with him. Only a few months before her death she had visited the United States, Japan, and Israel. Any account of her life would be incomplete without a reference to her social gifts. She was a born hostess. Those who had the privilege of being her fellow students in Manchester will still recall with pleasure her invitations to dances at Ashburne Hall, the Women's Hall of residence. Later in the succession of universities in which her husband was professor she took the deepest interest in the welfare of the wives and children of his staff. She seemed never to forget a name or a face. In association with her friend, the late Dr. Ida Smedley Maclean, she took an active part in the affairs of the University Womens Federation.

The full opportunity for her to exercise her great gifts came however in Oxford. There in her beautiful home or at Magdalen College she showed gracious hospitality both to Oxford friends and to the numerous visitors from home or overseas. No scientific conference in Oxford was complete without one of her delightful parties. Her unique qualities were recognised last year by the University of Oxford when they conferred upon her the Honorary Degree of Master of Arts. Her undoubted pleasure in receiving this degree was more than shared by her innumerable friends. She will be very widely missed and our deepest sympathy goes out to her husband and her daughter, Dr. Marion Robinson.

J. L. Simonsen.



Two indicator papers

for **pH** *determination*

UNIVERSAL One paper covering completely the range from 1 to 10 enabling pH values to be checked to within 0.5 pH.

COMPARATOR Four separate books for work requiring greater accuracy. With these papers the pH value of any solution can be ascertained to within0.3 pH.

Descriptive leaflet will be sent free on request.

JOHNSONS OF HENDON LTD

London, N.W.4

Est. 1743

We are makers of:

ALUMINIUM ISOPROPOXIDE

Samples and quotations from:

KAYLENE TERRA ITC ILLAYA BRAND

KAYLENE (CHEMICALS) LTD.

WATERLOO ROAD, LONDON, N.W.2

L. LIGHT & Co Ltd

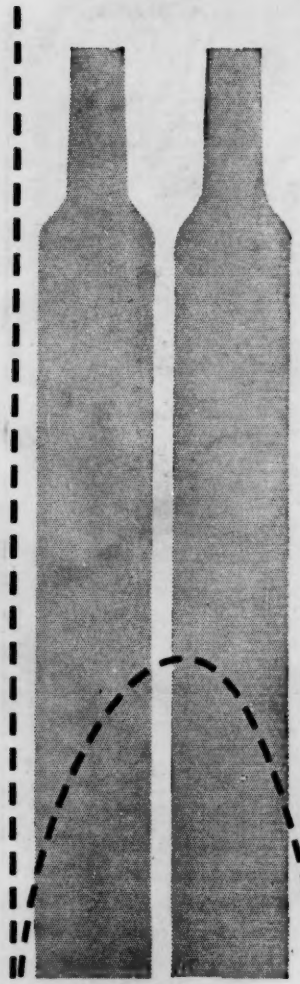
Latest additions to our 1954 catalogue

2 : 4-Dichlorobenzotrichloride	29/- H
3 : 4-Dichlorobenzotrichloride	36/- H
1 : 2-Dichloro-butene-3	36/- H
1 : 3-Dichloro-butene-2	12/- H
1 : 4-Dichloro-butene-2	38/- H
2 : 5-Diethoxy-tetrahydrofuran	24/- D
5-Diethylamino-2-aminopentane.	92/- H
N : N-Diethylamino-ethyl bromide HBr	17/- H
N : N-Diethyl cyclohexylamine	18/- H
Diethyl-dichlorosilane	6/- D
Di-2-ethylhexylamine	32/- H
Diethyl oxalopropionate	42/- K
Digitoxigenin (100 mg. amps.)	180/- d
1 : 4-Dihydroxy naphthalene	20/- H
3 : 4-Dimethoxy-toluene (methyl veratrol)	89/- K
1-Dimethylamino-2-propanol	6/- D
5 : 5-Dimethyl-barbituric acid	148/- H
2 : 5-Dimethyl-hexadiene-1 : 5	56/- H
5 : 6-Dimethyl-1 : 10-phenanthroline	8/- d
N : N-Dimethyl-*p*-phenylene-diamine oxalate	13/- D
2 : 8-Dimethyl-quinoline	34/- D
3 : 4-Dimethyl-6-*D*-ribityl-aminobenzene	4/- G
3 : 4-Dinitro-benzoic acid	12/- G
2 : 4-Dinitrotoluene	30/- K
2 : 6-Dinitrotoluene	7/- H
3 : 4-Dinitrotoluene	11/- H
2 : 4-Dioxythiazolyl-5-acetic acid (m. p. 169° C.)	35/- H
1 : 2-5 : 6-Di-*O*-*iso*propylidene glucofuranose	58/- H
Dodecyl benzene sodium sulphonate (80—85%)	15/- K
***iso*Durene** (1 : 2 : 3 : 5-tetramethyl benzene)	33/- G
Egg albumin, cryst. (ash <0·1%; moisture <6%; N = 13·8%)	150/- G
Ethyl-*n*-amyl ketone	18/- D
5-Ethyl-carbazole (m. p. 70° C.)	95/- H
S-Ethylethane-tetracarboxylate	15/- D
S-Ethylethene-tetracarboxylate	25/- D
5-Ethyl-2-methyl piperidine	42/- H
3-Ethyl-4-methyl pyridine (beta-Collidine)	18/- H
2-Ethyl-3-propyl acrylic acid	28/- H
Fluoro-acetamide (m. p. 107—9° C.)	240/- H
Fumaryl chloride	35/- H
Gallacetophenone (2 : 3 : 4-trihydroxy-acetophenone)	16/- D
Gitoxin (100 mg. amps.)	140/- d
Glyceric acid	25/- D
Hemicellulase	20/- D
Hemimellitic acid (benzene-1 : 2 : 3-tricarboxylic acid)	45/- D
1 : 1 : 1 : 2 : 2 : 3 : 3-Heptachloro-propane	16/- H
Hexachloro-2 : 5-cyclohexadien-1-one	42/- H
Hydroquinone di-*n*-butyl ether	20/- H
α-Hydroxyadipaldehyde (25% in H_2O)	22/- H
4-Hydroxy-3-nitro diphenyl	9/- D
5-Hydroxy quinoline	12/- G
2-Imino-4-oxythiazolyl-5-acetic acid (m. p. 248° C. dec.)	30/- H
α-Iodo-naphthalene	17/- D
Lactase	19/- D
Lactobionic acid, Ca salt	19/- D
β-Lactoglobulin, ex cow's milk, 3 × cryst. (ash <0·2%; moisture <5%; N = 15·6%)	70/- G
Lanthionine (50% each *L* and *meso*)	97/- G
Lipoxidase (100 mg. amps.)	39/- d
2-Methyl acridine	27/- D
Methyl-2 : 3-anhydro-4 : 6-O-benzylidene-α-D-allopyranoside	8/- G

POYLE TRADING ESTATE

COLNBROOK BUCKS ENGLAND

B.D.H. CONCENTRATED VOLUMETRIC SOLUTIONS



Presented in resilient polythene ampoules

Most of these solutions are now supplied in polythene ampoules which are for all practical purposes unbreakable.

They are easier to store, safer to handle and simpler to open. The accuracy of the solutions is unchanged, and so are the prices. As polythene is not inert to solutions of potassium permanganate, iodine, ceric sulphate or potassium dichromate these solutions will continue to be supplied in glass ampoules.

Please ask for price list

THE BRITISH DRUG HOUSES LTD.
B.D.H. LABORATORY CHEMICALS GROUP
POOLE DORSET
TELEPHONE: POOLE 962 (6 LINES)
TELEGRAMS: TETRADOME POOLE

BDH

CVS/LC/54

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.